

**THE INVESTIGATION OF THE RELATIONSHIP
BETWEEN THE DEPRESSION, ANXIETY, LEARNING AND
BIOLOGICAL RHYTHMS IN THE FRAME OF THE
PHOTOPERIOD, MATERNAL TRANSFER AND
SUPRACHIASMATIC NUCLEUS STUDIES**

FEVZİYE UMUT KIZILKAYA

JANUARY 2014

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by

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ABSTRACT

THE INVESTIGATION OF THE RELATIONSHIP BETWEEN THE DEPRESSION, ANXIETY, LEARNING AND BIOLOGICAL RHYTHMS IN THE FRAME OF THE PHOTOPERIOD, MATERNAL TRANSFER AND SUPRACHIASMATIC NUCLEUS STUDIES

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Some internal factors such as suprachiasmatic nucleus (SCN), pineal gland and melatonin hormone which play important role in the generation and the regulation of the rhythms as well as the environmental factors such as day length (photoperiod) are effective on mood states (anxiety and depression) and memory (spatial memory). However, in the literature, there was no comprehensive study which examines the reciprocal relationship among these variables and it was not known yet the practical and theoretical results of this study or relationship. In this planned thesis, these topics were investigated, related hypothesis were tested, new research models and techniques were implemented and the originality and the applicability of the results were

presented. The planned studies in this thesis were classified into 3 main topics: The investigation of the relationship among photoperiod, pineal gland and behaviors. Mood differences in different seasons were considered to be based on the different day lengths in these seasons. In the present study, the effects of different day lengths and pineal gland on mood (anxiety and depression) and spatial memory performance were investigated. Furthermore, whether or not these different day lengths had some effects on the infants through the maternal transfer were investigated. For this aim, **in the first study**, control (sham pinealectomized) and pinealectomized hamsters were used. Photoperiodic adult male and female Syrian hamsters (*Mesocricetus auratus*) were exposed to the long (18L), short (6L) and normal (14L) photoperiods for 14 weeks period. At the end of this period, anxiety (open field and elevated plus maze), depression (porsolt), and spatial memory (T-maze) tests were applied to the groups. In all tests, long photoperiod and pinealectomy reduced the anxiety, depression, and improved spatial learning in this study. We also found sex differences in these tests. **In the second study**, the juvenile hamsters borned to the mothers being exposed to these short, long and normal photoperiods were tested by the same experimental design when they were weaned. In this way, whether there was an effect of the maternal transfer on these behaviors or not were tested. In all tests, the behavior of the anxiety was transferred to the juveniles but not the depression, and spatial memory behaviors in this study. In mammals, SCN which located in the hypothalamus of the brain is responsible for the generation and the regulation of the circadian rhythms. **The third study** investigated, whether the electrolytic lesions of the SCN eliminate the variations of the behaviors such as anxiety, depression, and spatial memory in different time points of the day. This result could indicate for the first time that the circadian control of the behaviors via the SCN. For this aim, the rats coming from LD 12:12 photoperiod

were SCN lesioned. The anxiety, depression and memory experiments were performed in SCN lesioned, sham SCN lesioned and intact rats in different time points of the day (06:00, 12:00, 18:00 and 24:00). In such way, it were realized whether or not these behaviors had a circadian rhythm and this rhythm is controlled by the SCN. The results of the present study indicated that SCN lesions changed the circadian rhythms of the anxiety, depression, and spatial memory.

Keywords: Photoperiod, Pineal gland, Melatonin, SCN, Anxiety, Depression, Spatial memory, Syrian hamster, *Mesocricetus auratus*, Wistar Albino Rat, *Rattus rattus*

ÖZET

DEPRESYON, ANKSİYETE VE ÖĞRENME İLE BİYOLOJİK RİTİMLER ARASINDAKİ İLİŞKİNİN FOTOPERİYOD, MATERNAL TRANSFER VE SUPRAKİYAZMATİK NUKLEUS ÇALIŞMALARI ÇERÇEVESİNDE İNCELENMESİ

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Duygudurum (örn., kaygı ve depresyon) ve hafıza (örn., uzaysal hafıza) üzerinde suprakiyazmatik nukleus (SCN), pineal bez ve melatonin hormonu gibi içsel faktörler ile gün uzunluğu (fotoperiyod) gibi çevresel faktörlerin etkili olduğu bilinmektedir. Hipotalamusta bulunan suprakizmatik nucleus, biyolojik ritimlerin (mevsimel ve sirkadiyen (günlük yaklaşık 24 saatlik)) oluşturulmasında ve kontrolünde görev alır. Bu biyolojik ritimlerin düzenlenmesinde suprakiazmatik çekirdek ile pineal bez, melatonin hormonu arasındaki ilişki bilinmektedir. Ancak, literatürde, bu değişkenlerin duygudurum ile karşılıklı muhtemel ilişkilerini inceleyen kapsamlı bir çalışma bulunmamaktadır ve konunun kuramsal ve uygulamalı sonuçlarının neler olabileceği bilinmemektedir. Planlanan bu tezde, bu konular incelenmiştir; ilgili hipotezler test edilmiştir, yeni araştırma modelleri ve teknikleri sunulmuştur ve ortaya

ıkan sonuların orijinallięi ve deęiřik alanlarda uygulanabilirlięi gsterilmeye alıřılmıştır. Bu kapsamda planlanan alıřmalar 3 ana bařlık (alıřma) altında toplanmıřtır. Bu tezde; ilk olarak fotoperiyod, pineal bez ve davranıřlar arasındaki iliřki incelenmiřtir, ikinci olarak, bu evresel gn uzunluęu deęiřimlerinin maternal transfer aracılıęı ile doęum sonrası yavruda da etkilerinin olup olmadıęı incelenmiřtir, son olarak ise sıanlardaki SCN blgesi, elektrolitik lezyonlar ile ortadan kaldırıldıęında, gnn farklı zamanlarındaki anksiyete depresyon ve hafıza lmlerindeki farklılıkların neler olduęu arařtırılmıştır. Tm bu duygudurum ve deęiřkenlerin arasındaki iliřkiyi incelemek amacıyla, planladıęımız **birinci alıřmamızda**; kontrol (yalancı pinealektomili) ve pinealektomili (pineal bezi alınmıř) hamsterler kullanılmıştır. Fotoperiyodik (aktivitesini gn uzunluęuna gre dzenleyen) bir tr olan Suriye hamsterleri (*Mesocricetus auratus*) uzun (18L), kısa (6L) ve normal (14L) fotoperiyotlara yerleřtirilmiřtir ve 14 hafta bu fotoperiyodlara maruz bırakılmıştır. Bu srenin sonunda her iki gruptaki hamsterlere anksiyete (aık alan ve ykseltilmiř + labirent), depresyon (Porsolt) ve hafıza (T-Maze) testleri uygulanmıřtır. Birinci alıřmamızdaki sonulara gre, uzun fotoperiyoda maruz kalma ve pineal bezin ıkarılması, deneklerin hem kaygı ve depresyonun azalmasına hem de spasyal hafıza performanslarının iyileřmesine katkı saęladıęı bulunmuřtur. **İkinci alıřmamızda** ise, birinci alıřmamızda kulladıęımız hem pineal bezi alınmıř hemde uzun, kısa ve normal fotoperiyodlara maruz bırakılmış anne hamsterlerden doęan yavrular ile hibir cerrahi mdahalede bulunmadıęımız fakat  farklı fotoperiyoda maruz bıraktıęımız anne hamsterlerden doęan yavrular stten kesildikten sonra, aynı davranıř testleri uygulanmıřtır ve bylece bu davranıřlarda maternal transferin bir etkisinin olup olmadıęı test edilmiřtir. Yaptıęımız testlerden, annelerdeki kaygı bilgisi yavrulara daha kolay aktarılırken, depresyon ve ęrenme gibi daha kompleks

davranışların yavruya aktarılmasının daha zor olduğu bilgisine ulaşılmıştır. Üçüncü ve **son çalışmamızda ise**, LD 12:12 fotoperiyodunda tutulan Wistar Albino (*Rattus rattus*) sıçanlardan 3 farklı grup oluşturulmuştur. İlk grup, SCN bölgesinde elektrolitik lezyonlar oluşturulan sıçanlar ikinci grup yalancı-SCN lezyonlular ve son grupta ise intakt (hiçbir operasyona tabii tutulmamış sıçanlarda oluşmaktaydı. Cerrahi operasyonlardan 1 hafta sonra anksiyete, depresyon ve öğrenme testleri (Morris Water Maze) günün farklı zamanlarında (06:00, 12:00, 18:00 ve 24:00) gerçekleştirilmiştir. Böylece bu davranışların sirkadiyen ritimlerinin olup olmadığı ve eğer var ise bunun SCN tarafından kontrol edilip edilmediği anlaşılmış olacaktı. Yaptığımız bu son çalışmanın sonucuna göre suprakiazmatik çekirdeğin, kaygı depresyon ve spasyal hafıza performanslarının sirkadiyen ritmi üzerinde değişikliklere sebep olduğu gösterilmiştir. Sonuç olarak lezyonlu grupların kaygıları düşük olmasına rağmen bu eğilimin öğrenmede aynı yönde olmadığı görülmektedir.

Anahtar Kelimeler: Fotoperiyod, Pineal bez, Melatonin, SCN, Anksiyete, Depresyon, Uzaysal hafıza, Suriye hamster'i (*Mesocricetus auratus*), Wistar Albino Sıçan (*Rattus rattus*)

TO MY SUPERVISOR AND MY MOTHER

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1. INTRODUCTION

1.1. PHOTOPERIOD

Photoperiodism is the ability of plants and animals to measure environmental day length (photoperiod), a process that lie behinds the called biological calendar (Nelson et al., 2010). The measuring day length biological ability of organisms provides themselves to understand the time of year and engage in seasonally suitable adaptations. Individuals that respond to day length can certainly understand the time of year according to just two bits of data: (1) the length of the daily photoperiod and (2) whether day lengths are increasing or decreasing (Walton et al., 2011). Changes in day length provide the most error-free indication of time of year, thus facilitate to guess seasonal conditions. The environmental variation that controls the phenotypic course is important in teasing out the interaction between environment and genes which drives phenotype which is the result of interactions between genes and environment (Walton et al., 2011). In the wild, day length mostly identify the phenotype of new born small vertebrates (Boonstra, 1989; Ergon et al., 2001; Gundersen and Andreassen 1998). In mammals, photoperiodic information can even be passed to developing fetuses in utero thus the summer or winter phenotype may begin to develop before birth (Weaner et al., 1987).

In mammals, hamster and sheep are often used in such studies, because they also show robust photoperiodic responses. The pineal gland and its hormone melatonin, mediates photoperiodic time measurement in mammals (Hazlerigg, 2010; Makino et

al., 2001). Pinealectomy inhibit responsiveness to photoperiod in every mammalian (Hare, 1978). Recent studies have now identified several rodent species that exhibit changes in affective behaviors that are stimulated by changes in photoperiod. Exposure to short days increases anxiety-like and depressive-like responses in some rat species (Weil et al., 2007) and Siberian hamsters (Prendergast and Nelson, 2005; Pyter and Nelson, 2006). Short-day aggravation of depressive-like and anxiety-like behaviors have been reported in both nocturnal rodents (Benabid et al., 2008; Molina-Hernandez and Tellez-Alcantara, 2000; Prendergast and Kay, 2008) and diurnal rodents (e.g., Nile grass rats (Ashkenazy-Frolinger et al., 2010) and sand rats (Ashkenazy et al., 2009). These affective responses to short days are clearly linked directly to pineal melatonin secretion duration (Ashkenazy et al., 2009). These behaviors are influenced not only by acute short-day photoperiod exposure as well by prenatal melatonin exposure in utero. It was suggested that photoperiodic exposure of mother during gestation may regulate the developing brain through exposure to the melatonin rhythms which effects adult affective responses (Workman et al., 2008). Short-day photoperiod induction of anxiety- and depressive-like behaviors is connected with elevated serotonin transport in the mid brain, consistent with the therapeutic use of serotonin-reuptake inhibitors to combat anxiety and depression in humans (Benca et al., 2009).

Photoperiod can also modulate learning and memory, possibly as a functional result of altered hippocampal morphology. Seasonal variation in hippocampal and brain volume is positively influence seasonal navigation and spatial memory requirements (Lavenex et al., 2000; Yaskin, 2009). Seasonal region maintenance life history has positively relationship with photoperiodic variation in spatial learning and memory, providing to sex and population based differences in spatial learning and memory performance across seasons (Galea et al., 1996; Galea et al., 1994). When

male white-footed mice, are bought into lab where there are no territories to maintain, a similar decrease of hippocampal volume observed during winter in the wild is observed in laboratory short days (Pyter et al., 2005), showing an underlying photoperiodic mechanism in brain morphological plasticity.

In summary, circadian rhythms and ambient photoperiod effect cognition and affective behavior through multiple mechanisms, involved regulation of noradrenergic innervation of the cortex, clock gene expression in the SCN and hippocampus, serotonin transport and dendritic spine density.

1.2. PINEAL GLAND

The pineal gland is unique neuroendocrine organ located in the midline of the brain. Since ancient times, the pineal gland was called ‘enigmatic organ’ by Van Gehuchten (1937). According to the Indian traditions, humans would be equipped with a ‘third eye’ or mystical organ (pineal gland), corresponding to the sixth chakra (ajna) which would supply a window into the spiritual life of individuals and would cover the key to its mental power (Baker, 1985). One of the most prominent proponents of the role of the pineal gland was the French philosopher Rene Descartes (1596-1650), who suggested as the physical seat of the human soul (Lopez-Munoz et al., 2011). Finally, the major scientific advances about the role of pineal gland and its secretion melatonin that have come out the middle of the 20th century. The primary function of pineal gland to transduce light/dark information to whole body physiology via releasing melatonin (Arendt, 2005). The pineal gland adrenergic innervation, which activates a cascade of circadian events that leads to the nightly formation of melatonin from serotonin and the pineal, is also innervated by parasympathetic system (Larsen, 1999); the role and regulation of which are presently unclear. The removal of the pineal

gland (pinealectomy) abolishes the rhythmic endogenous melatonin release and decreases the plasma levels of melatonin significantly (Hoffman and Reiter, 1965). The pineal gland is correlated to the central rhythm generator in the suprachiasmatic nucleus of the hypothalamus via multi-synaptic pathway. The SCN-pineal cycle is one of the most well understood neuronal circuits of brain. Because pineal gland is bilaterally innervated by the two superior cervical ganglions, a partial injury to the circuit can be performed to allow examination of functional recovery from partial nerve lesions (Zigmond et al., 1981). In addition to this information, Zigmond laboratory have indicated that pineal gland recovers fully within two days after the loss of 50% of its adrenergic input (Kuchel and Zigmond, 1991; Zigmond et al., 1981) but no recovery is seen following a partial decentralization of the pineal by denervating one of the two superior cervical ganglions (Zigmond et al., 1985). Circadian rhythms of melatonin synthesis and secretion are abolished after bilateral SCN lesion, demonstrating that SCN is the melatonin rhythm generator (Kalsbeek et al., 2000).

1.3. MELATONIN HORMONE

Lerner and co-workers first isolated and discovered melatonin (5-methoxy-N-acetyltryptamine) in the late 1950s (Lerner et al., 1958, 1959, 1960). Melatonin is known as a substance involved in the processing of photoperiodic information in various organisms, from unicellular to human. In reptiles, melatonin induces photoaggregation of skin pigments. In vertebrates melatonin is mainly produced and secreted by the pineal gland though it is also produced in small amounts in other tissues, such as gastrointestinal tract (Reiter, 1991., Huether, 1993) and retina (Zawilska and Nowak., 1992), thymus, bone marrow, respiratory epithelium, skin, lens and in other sites (Pandi-Perumal SR et al., 2006; Lerner et al., 1958).

The amphiplicity of the melatonin is allowing the molecule to pass by diffusion from peripheral circulation to other fluids or cells (Poeggeler et al., 1994). 70% melatonin is bound to albumins in serum the remaining 30% diffuses to the surrounding tissues (Hardeland R et al., 2006). Precursors of melatonin are tryptophan and serotonin. Two enzymes which are N-acetyltransferase (AANAT) and hydroxyindole-O-methyltransferase (HIOMT) involved in its synthesis. AANAT, the first-rate limiting enzyme in melatonin production, converts serotonin to N-acetylserotonin (NAS), HIOMT converts NAS to melatonin (figure 1). By the axons of retinal ganglion cells running in the optic nerves and forming the retino-hypothalamic tract, light-dark cycle acts on the neuronal activation of the anterior hypothalamus which also controls the regulation of the melatonin synthesis. Postganglionic sympathetic fibers on the surface of pinealocyte membrane release norepinephrine. It stimulates adrenoreceptors leading to cAMP formation as well as other second messengers, which stimulate the expression and activity of AANAT.

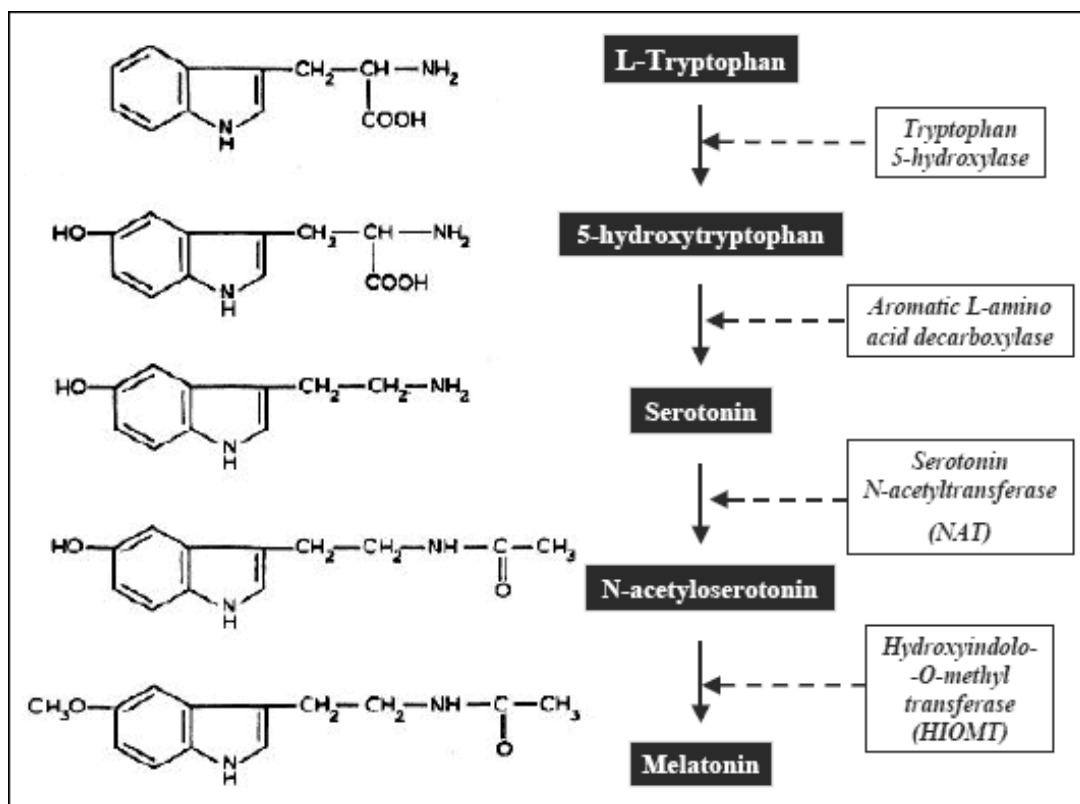


Figure 1. Metabolic pathway of melatonin synthesis

Melatonin is secreted with a strong daily rhythm, peaking close the middle of the night. Throughout the daytime, concentrations of melatonin keep very low, as exposure to light strongly repress its secretion in an intensity-dependent manner (I. M. McIntyre et al., 1989). Therefore melatonin is a signal of darkness that encodes time-of-day and length-of-day information to the brain including the suprachiasmatic nucleus, brain and peripheral organs (Pandi-Perumal et al., 2006b).

Melatonin has been implicated in circadian regulation of several biological processes, such as sleep, mood, behavior, visual, reproduction, neuroendocrine and also affects the immune system and aging (Arendt J., 2000; Borjigin, J et al., 1999; Brzezinski, 1997; Masana and Dubocovich, 2001., Vanecek, 1999; Wirz-Justice, 2001). Additionally, its neuroendocrine functions, many pharmacological effects of melatonin, have been reported in rodents, such as sedative, analgesic anticonvulsant

and anxiolytic activities (Albertson et al., 1981; Datta and King 1977, 1979; Golombek et al., 1993; Golus and King, 1981; Sugden, 1983).

The anxiolytic-like effects of melatonin have usually been described in experimental situation such as the passive avoidance test, the open field or the elevated plus maze, which are limited situations stimulating “state” anxiety (Lister, 1990). Melatonin has revealed anxiolytic effects in both preclinical (Crupi et al., 2010; Golombek et al., 1993; Golus and King, 1981; Papp et al., 2006) and human studies (Caumo et al., 2009; Srinivasan et al., 2006) and recently, the non-selective MT₁/MT₂ receptor agonists agomelatine and Neu-P11 have been shown to possess anxiolytic properties in preclinical models of anxiety (Millan et al., 2005; Rainer et al., 2011; Tian et al., 2010).

The previous reports showed that melatonin induces an anxiolytic-like effect in the elevated plus maze by increasing the time spent in the open arms (Golombek et al., 1993) and in novelty-suppressed feeding by decreasing the latency to eat (Crupi et al., 2010). Despite of the anxiolytic properties of melatonin in the elevated plus maze and novelty-suppressed feeding, Ochoa-Sanchez R. et al., (2012) did not find any effect of melatonin in the open field test. In contrast, Golus and King (1981) found that melatonin increased the activity within the central area of the open field test. This disagreement may be due to the different experimental protocols used. There are inconsistent data about anxiety in the literature, so we investigated effects of pinealectomy, melatonin, and circadian rhythms on the anxiety-like behavior.

In a point of behavioral process, specific receptors and binding sites for melatonin have been melatonin receptors (M₁/M₂) have been found in the areas involved in cognition and memory in the brain (Cardinali et al., 1979; Weaver et al., 1989). Melatonin receptors are located in the hippocampus of several mammals. MT₁

and MT₂ receptors exist in dentate gyrus, CA3 and CA1 areas and subiculum of the hippocampus (Mushoff et al., 2002). Individual endogenous melatonin levels associated with parahippocampal activation and is not further affected by exogenous melatonin. These information demonstrate us memory is interested in activation in the hippocampus and parahippocampus are affected by the time of day and melatonin in a differential manner and may include the circadian clock and melatonin in human memory processing during the night (Gorfine and Zipas, 2007).

Another study shows that melatonin improves learning and memory performances and, to modulate neural plasticity by regulating Neural Cell Adhesion Molecule (NCAM) expression in the brain, impaired by hyperhomocysteinemia in rats (Baydas et al., 2005). Melatonin decreases recognition time and leads to a facilitation of short term memory (Argyriou et al., 1998), as well as exerts beneficial effects upon learning performance (Baydas et al., 2005). Nevertheless, contradictory evidence was also present in the literature. A more recent research has indicated that low dose of melatonin given from weaning did lead to learning and memory deficit in rats (Cao et al., 2009). This difference in above mentioned findings can be due to some related factors (e.g., test, measurement, model or paradigm, dose differences, and etc.). For example, the former studies used different learning paradigm such as active and passive avoidance test (Martini, 1971; Kovács et al., 1974), whereas the latter one (Cao et al., 2009) employed the Morris water maze. This important difference can be attributed to the Morris water test that has been considered to be affected by both some exogenous factors (nutrition procedure, stress, infection, and etc) and endogenous factors (i.e., sex, age, strain differences) (Hooge and De Deyn, 2001). Another important reason for preferring the Morris water test is that it is one of the most suitable

tests for the investigation of spatial memory (Hooge and De Deyn, 2001). Since our focus was on spatial memory, we used the Morris water maze test.

Furthermore, melatonin affects other processes such as depression, stress-and-anxiety-related behaviors. The rhythm of melatonin secretion may be impaired in various pathological states and an alteration in its secretory pattern has been found in some psychiatric disorders.

Supporting proof of relationship between the pineal hormone, melatonin, and depression has been collected in patients since 1980s. The first arresting clue for this was decreasing of nocturnal serum concentrations of melatonin in depressed patients in comparison with control subjects (Wetterberg, 1983; Beck-Friis et al., 1984). In addition to this information, melatonin was also proposed to be an inhibiting factor of corticotrophin releasing factor during depression, showing the possibility that melatonin may play a role in the etiology of depression (Beck-Friis et al., 1985). Accordingly, exogenous administration of melatonin was found to be effective against winter depression and sleep disturbances in major depressive disorder.

Melatonin is shown to produce antidepressant-like effect in the mouse tail suspension test (Mantovani et al., 2003; Prakhie and Oxenkrug, 1998), and in the rat forced swimming test (Micale et al., 2006). Another study indicated that melatonin administration prevent behavioral and physiological changes induced by the chronic mild stress model of depression in mice (Detanico et al., 2009), hence reinforcing cue that this hormone possess antidepressant properties and is effective in animal models of depression. Shaji and Kulkarni, (1998) indicated that melatonin was shown to reduce the duration of immobility in the forced swim test.

1.4. CIRCADIAN RHYTHMS AND SUPRACHIASMATIC NUCLEUS

We sustain our life in rhythmic world. Seasonal rhythms in bright volume, ambient temperature, humidity and more occur with the rotation of earth around itself and around the sun. To the best way to adapted these rhythms, most organisms developed rhythms in almost every direction of their body, ranging from gene expression, physiology (e.g., heart rate, metabolism and hormone secretion), cognitive functions (e.g., learning and memory) and activity – rest patterns (Kronfeld-Schor and Einat 2012). Rhythms that approximate the 24-h dark-light cycle is called circadian (from circadiem) rhythms, whereas cycles that is shorter or longer than the 24-h cycles are referred to ultradian and infradian rhythmicity, respectively.

Animals expose to very different environmental conditions because being active at different times, on diel or seasonal scale. As a result of these different adaptations, the environment of an organism is divided into times when it is optimal to perform a certain activity and times when performing the same activity may even be disadvantageous. Most of earliest mammals were nocturnal (Crompton, 1980) although humans are one of the species which developed to be active during the daytime.

To optimally adapt to the rhythmic world, species have an internal circadian timing system, contain a master clock which in mammals is located in the Suprachiasmatic nuclei (Klein et al., 1991; Moore-Ede et al., 1982). SCN which has circadian pacemaker is located anterior part of hypothalamus. SCN controls most of physiological and behavioral variables through the orchestrated function of clock control genes that regulate the output rhythms throughout the central nervous system and periphery. SCN creates circadian rhythms via a set of positive and negative feedback loops of transcription and translation (Mendoza and Challeng, 2009; Welsh

et al., 2010). This pacemaker can be reset by environmental light (Meijer, 2001) and coordinates in adaptive synchrony both behavioral and physiological rhythms that emphasize an organism's activity during the day (Green and Menaker, 2003). The SCN is itself synchronized with the day/night cycle by direct neural input from specialized retinal photoreceptors (Berson et al., 2002; Berson, 2003).

Repairing itself, not to respond, and changing environment is provided by this internal timing system for the individual and also, it allows him/her/it, to choose the right time for a given response or activity without being easily misdirected by little environmental changes. In addition that, it makes individual to guarantee that a temporal order between internal process and between them and the environment maximizes performance (Kronfeld-Schor and Einat, 2012).

Circadian rhythmicity in a diverse of endocrine, behavioral and biochemical processes are disturbed by lesions of the SCN (Moore and Eichler, 1972; Stephan and Zucker, 1972; Turek, 1985). In place of this, SCN cells transplanted to SCN-lesioned animals restore circadian rhythms (Drucker-Colin et al., 1984; Ralph et al., 1990; Sawaki et al., 1984). Significantly, the transplanted animals take on characteristics of the donor's biological rhythms (Sollars et al., 1995). Although, recent studies show that lesions of the SCN do not remove peripheral circadian rhythms (Grundschober et al., 2001; Guo et al., 2005), peripheral oscillators demonstrate disrupted phase synchrony in the absence of SCN influence. Therefore, SCN appears to be required for the coordination, but not for the maintenance, of peripheral circadian oscillations.

Diurnal rhythms of melatonin secretion are controlled by a complex cascade of neurotransmission originating in the SCN. Throughout daytime, a synaptic input from GABAergic SCN terminals to autonomic Paraventricular (PVN) neurons (Buijs et al., 2003; Teclemariam-Mesbah et al., 1999) enables the SCN to block the glutamatergic

inputs from PVN. The resulting effect on the preganglionic sympathetic neurons in the intermediolateral nucleus of the spinal cord (Kannan et al., 1989) prevents melatonin production throughout the day (Kalsbeek et al., 2000).

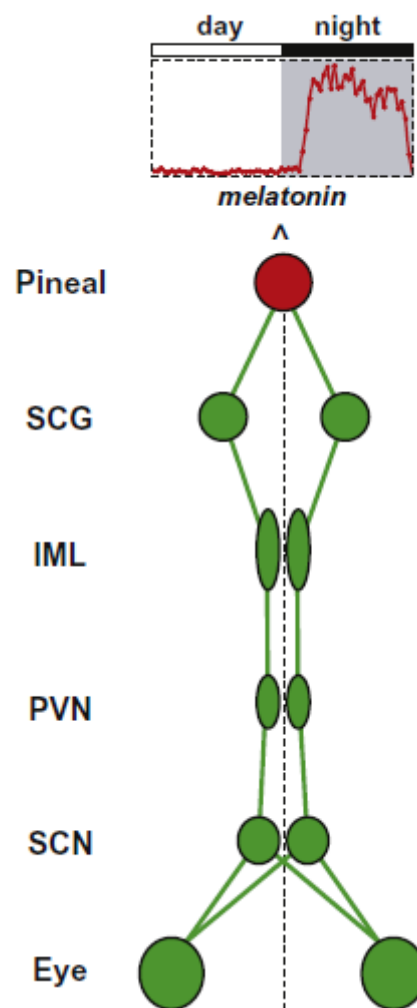


Figure 2. The neuronal circuit that controls pineal rhythmicity. SCG: superior cervical ganglion; IML: intermediolateral nucleus of the spinal cord; PVN: paraventricular nucleus of the hypothalamus; SCN: suprachiasmatic nucleus. (Borjigin, et al., 2012)

At night, glutamatergic SCN output innervating PVN (Hermes et al., 1996) stimulate melatonin synthesis in pineal gland (Perreau-Lenz et al., 2004) whereas melatonin synthesis is activated by the release of norepinephrine from the superior cervical ganglion (Drijfhout et al., 1996a,b). Norepinephrine release can be powerfully inhibited by light (Drijfhout et al., 1996b) via the release of glutamate in the SCN (Ebling, 1996) from nerve ending of the retino hypothalamic tract the axon bundles of the melanopsin-containing retinal ganglion cells (Guler et al., 2008).

The effect of biological changes stimulated by the asynchronies of circadian rhythms can be seen in conditions of shift work or jet-lag (Wagner, 1999) but the impact of impairments of circadian rhythms on emotional behavior is less clear. In rodents, changes in the phase period or amplitude of hypothalamic-pituitary-adrenal axis hormones, melatonin, locomotor activity, body temperature have been observed in several models of depression (Ninan et al., 1998; Shiromani and Overstreet, 1994; Solberg et al., 2001). SCN lesions (Arushanian and Beier, 1999) or a mutation of cAMP-responsive element modulator (Maldonado et al., 1999) were indicated to change levels of anxiety and locomotor activity. A mutation of circadian gene-clock – causes to rising exploratory behavior and activity-based stimulation in the open field test and in the elevated plus maze test, however is not limited to emotional component of arousal that is revealed by new and stressful environments produced in the elevated plus maze (Clenet et al., 2006). On the other hand, dysfunction of the clock gene does not cause to depressive-like in the forced swimming test (Clenet et al., 2006). In a study of Easton et al., (2003) asserted that clock function may affect anxious behavior in some cases but does not have a common nor permanent effect on anxiety.

Recent studies have indicated that the disruption of the core proteins in the master circadian clock can trigger mania-like behaviors (Roybal et al., 2007) and clock-related genes with mood disorders (Benedetti et al., 2005a,b).

The components of the molecular clock are widely expressed throughout brain and ability of these genes between transcriptional activators and repressors suggest that they could orchestrate circadian control of neuronal gene expression and neuronal activity by influencing the function of neurotransmitter and receptors involved in regulation of emotion and cognition (Benca et al., 2009). For instance, projections from suprachiasmatic nucleus to locus coeruleus (LC) make possible circadian regulation of noradrenergic activity and are important circadian regulation of sleep-wake cycle (Gonzalez and Aston-Jones et al., 2002) and synaptic plasticity including long-term potentiation (Chaudhury et al., 2005; Chaudhury and Colwell, 2002). However, in prenatal rats, activation of dopamine receptors resets the developing circadian pacemaker (Shearman and Weaver, 2001), in adult rodents, activation of serotonin receptors, either 5-HT_{1A}, 5-HT₂, or 5-HT₇ receptor subtypes, resets the phase of suprachiasmatic nucleus circadian pacemaker (Tominaga et al., 1992; Gannon and Millan 2006; Ehlen et al., 2001; Duncan et al., 2004). These studies illustrate that the clock genes-mediated interaction with neurotransmitter and the SCN-mediated circadian clock outputs and other neural process is confused and probably act a part in the regulation of broad range of behaviors containing emotions, being awake, motivation and cognition.

1.5. ANXIETY

Anxiety is a physiological and psychological state characterized by unpleasant emotional state, fear and distressing physical symptoms in response to stressors.

Anxiety disorders represent a public health problem with a life time prevalence of 16.6 % (Somers et al., 2006) and in the pediatric populations, anxiety disorders are quite common with prevalence estimates ranging from 5 to 18% (Ramsawh et al., 2010). Therefore, there is an expanding interest discovering peculiar pharmacotherapeutic targets for the treatment of anxiety. The neurohormone melatonin modulates many physiological functions such as circadian rhythms, mood, sleep and reproduction (Reiter 1991; Simonneaux and Ribelayga, 2003). Additionally, its neuroendocrine functions and also, melatonin has been related to stress and anxiety (Caumo et al., 2009; Rios et al., 2010). Melatonin has revealed anxiolytic effects in both preclinical (Crupi et al., 2010; Golombek et al., 1993; Golus and King, 1981; Papp et al., 2006) and human studies (Caumo et al., 2009; Srinivasan et al., 2006). The non-selective MT₁/MT₂ agonist agomelatine and Neu-P11 have been demonstrated to possess anxiolytic properties in preclinical models of anxiety. Photoperiodic conditions can also regulate affective behaviors. For example, hamsters exposed to short-days early in life have increased anxiety- and depressive-like responses as adult (Pyter and Nelson, 2006).

1.6. DEPRESSION

Depression is a state of low mood and reluctance to activity that can affect a person's thoughts, behavior, feelings and sense of well-being. Depression influences 17-20 % of the global population with major outcomes for society (Kessler et al., 1994) and possible occurrence of depression episode at any age from childhood to elderly.

Depressive disorders are defined by behavioral, psychological and physiological changes, bearing feelings of hopelessness, anhedonia and guilt, suicidal opinion, distortion of sleep and appetite as well as cognitive function (Cryan et al., 2002).

Historically, many different theories have been proposed to explain pathophysiology of this disease. The most important has been the hypothesis claiming lack of monoamines and most particularly is serotonin (5-hydroxytryptamine, 5-HT). At the level of pineal gland and principally at this level in the brain, serotonin is converted to melatonin, a neurohormone crucial for regulation on circadian cycles. Dysregulation of circadian cycles turns out to be one of the main features of depression (Lanfume et al., 2013). Many ways of evidence in humans as well as in animal models obviously show connection between depression and circadian rhythms. Disease patterns, mechanisms and models; treatment effects in patients and in animal models are base of evidences. A majority of studies examined the interactions between depression and activity level across the day/night cycle. These studies demonstrated changes in activity patterns of depressed patients. For instance, depressed patients reduced activity levels during wake time and to demonstrated higher motor activity during sleep (Volkers et al., 2003). Furthermore, chronic exposure to light at night through shift work is associated with higher prevalence of mood disorders (Dumont and Beaulieu, 2007). Elevated exposure to light at night correlates with increasing rates of depressive disorders. Circadian clock is frequently phase-delayed in major depressive disorder, with intensity of depression associating with extent of delay (Emens et al., 2009). Circadian abnormalities are important in depressive disorder.

There is bidirectionally the relationship between depressive-disorder and circadian system. To date, the hypothesis that depression may be related to abnormalities in the biological clock clearly stands side by side with other major putative causes of this disease (Lanfume et al., 2013).

1.7. SPATIAL MEMORY

Spatial memory is an essential part of our ability to function as an individual within our environment and its spatial orientation. For instance, a person's spatial memory is required to navigate around a knowing city, just as a rat's spatial memory is needed to learn the location of food at the end of a maze. When learning to navigate their environments, humans and rodents similar realize distinct cognitive strategies that are mediated by interacting brain structures (McDonald and White, 1994; Packard and McGaugh, 1996). Various extrinsic and intrinsic factors affect the choice of learning strategy used by rodents, including cue salience, training level, biological sex, hormonal profile, and emotional status (Chang and Gold, 2004; Hawley et al., 2011; Hawley et al., 2012; Hawley et al., 2013; Kanit et al., 2000, Korol et al., 2004; Wingard and Packard, 2008).

The learning strategies used during spatial navigation have been linked with distinct neuronal networks. For instance, place learning, known as hippocampus-based navigational strategy, in which distal cues are used as guides (Maguire et al., 1995; Morris et al., 1982) and the striatum guides the expression of response and stimulates-response strategies, which are based on either egocentric information such as body movement (Packard and McGaugh, 1996; DeCoteau and Kesner, 2000), or striking visual cues proximal to goal that mark its location (McDonald and White, 1994). In addition, sex differences have been found in the strategies used to found a hidden goal in spatial environments. For instance, male rats are better than females using spatial strategy based on place learning (Blokland et al., 2006) and there is a robust relationship between ovarian hormonal status and learning strategy in adult female rodents (Daniel and Lee, 2004; Pleil and Williams, 2010).

Adult mammalian brains are capable of some structural plasticity. In spite of that the basic cellular mechanisms underlying learning and memory are being elicited, extrinsic factors contributing to this plasticity remain unspecified (Walton et al., 2011). Some species, such as birds and white-footed mice show seasonal changes in structure and function of the hippocampus induced by a distinct environmental signal, photoperiod. Changes in brain morphology in white-footed mice following exposure to short day lengths are accompanied by disrupted spatial memory and learning in the Morris water maze (Pyter et al., 2005a, 2006; Workman et al., 2009). In addition, spatial learning and memory is correlated with hippocampal long-term potentiation (Shapiro and Eichenbaum, 1999; Lynch, 2004) and long-term potentiation can be modified by day length (Walton et al., 2011). Day length is also encoded by the nightly duration of pineal melatonin secretion. Though, the exact role of melatonin on hippocampal function remains unclear, several studies have demonstrated that pharmacological treatment with melatonin blocks long-term potentiation in the CA1 area of the hippocampus (Feng et al., 2002; Talaei et al., 2010). In contrary, melatonin decrease recognition time and leads to a facilitation short-term memory (Argyriou et al., 1998). Therefore it would be an interesting research inquiry of how the melatonin has an effect on the spatial memory performance of rats.

2. OBJECTIVES

In the first study, the aim was to investigate how the behaviors, such as anxiety, depression and learning are affected by the different day lengths. Pineal gland plays an active role in photoperiodic regulations. In a limited number of studies in the literature, it is suggested that depression and anxiety may show some seasonal changes but the effect of pineal gland has not been shown yet. This study was carried out with Syrian hamsters (*Mesocricetus auratus*). Since this hamster performs its physiological regulations as regards photoperiod, study which is observed photoperiod effects is especially preferred. Also, the effect of different day length on learning and memory has not been investigated before. In this regard, our study is important in terms of the developing anxiety and depression related information available in the literature and revealing for the first time photoperiod effect on learning.

In addition to that, in the literature, it is demonstrated that environmental day length information is transmitted from mother to offspring during pregnancy (maternal transfer) and this information regulates offspring development in the pregnancy and after the birth. However, it has not been known that whether the maternal transfer influence on after the birth offspring behavior or not (anxiety, depression and memory). **In the second study**, the maternal transfer of these behaviors will be examined in juvenile Syrian hamsters.

In mammals, some parameters of endogenous circadian rhythm (e.g., locomotor activity, body temperature, and release of some hormones) are generated and controlled by a circadian oscillator, located in the hypothalamic Suprachiasmatic

nuclei (SCN). These circadian rhythms disappear by the ablation of the SCN. **In the third study**, the effects of SCN lesions on the anxiety-like behavior, depression and spatial memory performance of the Wistar albino rats were investigated. The animals were tested by open field and elevated plus maze tests for anxiety-like behavior, forced swim test for depression and Morris water maze test for spatial memory.

3. MATERIALS AND METHODS

3.1. Animal Care

Adult male Wistar rats (200 – 250 g) and Syrian hamster (80 - 100g) were obtained from our laboratory colony maintained at the Abant Izzet Baysal University (AIBU). Rats were exposed from birth to 12L (12 hour of light, 12 hour of darkness, lights off at 18:00 hr). Controls hamsters were exposed from birth to 14L (14 hour of light, 10 hour of darkness, lights on 06:00; lights off at 20:00 hr). Hamster were exposed to long photoperiod (18 hour of light, 6 hour of darkness, lights on 06:00; lights off at 24:00 hr). Hamster were exposed to short photoperiod (6 hour of light, 18 hour of darkness, lights on 06:00; lights off at 12:00 hr). Animals were maintained in plastic cages (16x31x42 cm) with pine shavings used as bedding. All cages exposed to 200 lux light .Food pellets and tap water were accessible ad libitum. The procedures in this study were carried out in accordance with the Animal Scientific procedure and approved by the Institutional Animal Care and Use Committee. All lighting was provided by the cool-white fluorescent tubes controlled by automatic programmable timers. Ambient temperatures in the animal facilities were held constant at 22 ± 2 °C in air-ventilated rooms.



Figure 3. Syrian hamster



Figure 4. Wistar albino rat

3.2. Experimental Protocol 1

In the first study, the ninety six adult hamsters were used and were randomly divided into two group as control (sham pinealectomized) and pinealectomized hamsters. In sham pinealectomy, animals were exposed to the same surgical procedure with the experimental group except for the removal of the pineal gland. Photoperiodic Syrian hamsters (*Mesocricetus auratus*) were exposed to the long (18L), short (6L) and normal (14L) photoperiods for 14 weeks period. At the end of this period, anxiety (open field, elevated plus maze), depression (porsolt) and spatial memory (t maze) tests were implemented to the all groups. All test were applied to between ct 8 and ct 11 hours.

Experimental protocol 1

Control (n:48)

24 male ve 24 female hamster



Groups

- | | | | |
|-----------------------|-------|----------------|-------|
| 1) Long photoperiod | (18L) | Male hamster | (n:8) |
| 2) Long photoperiod | (18L) | Female hamster | (n:8) |
| 3) Short photoperiod | (6L) | Male hamster | (n:8) |
| 4) Short photoperiod | (6L) | Female hamster | (n:8) |
| 5) Normal photoperiod | (14L) | Male hamster | (n:8) |
| 6) Normal photoperiod | (14L) | Female hamster | (n:8) |



14 Week

Applied Tests

Anxiety
Open Field
Elevated Plus Maze

Depression
Porsolt

Learning and Memory
T-Maze

Pinealectomy (n:48)

24 male ve 24 female hamster



Groups

- | | | | |
|-----------------------|-------|----------------|-------|
| 1) Long photoperiod | (18L) | Male hamster | (n:8) |
| 2) Long photoperiod | (18L) | Female hamster | (n:8) |
| 3) Short photoperiod | (6L) | Male hamster | (n:8) |
| 4) Short photoperiod | (6L) | Female hamster | (n:8) |
| 5) Normal photoperiod | (14L) | Male hamster | (n:8) |
| 6) Normal photoperiod | (14L) | Female hamster | (n:8) |



14 Week

Applied Tests

Anxiety
Open Field
Elevated Plus Maze

Depression
Porsolt

Learning and Memory
T-Maze

3.3. Experimental Protocol 2

In the second study; juvenile hamster borned to the mothers and fathers being exposed to these long,short and normal photoperiods in the first study were tested by the same experimental design when they were weaned.

Control (n:48)

24 male ve 24 female hamster



Mating



Hamster pups
Male (n:24) Female (n:24)



Weaning (21. Day of birth)

Applied Tests

Anxiety
Open Field
Elevated Plus Maze

Depression
Porsolt

Learning and Memory
T-Maze

Pinealectomy (n:48)

24 male ve 24 female hamster



Mating



Hamster pups
Male (n:24) Female (n:24)



Weaning (21. Day of birth)

Applied Tests

Anxiety
Open Field
Elevated Plus Maze

Depression
Porsolt

Learning and Memory
T-Maze

3.4. Experimental Protocol 3

In this study, sixty adult male Wistar rat were used and were randomly divided in to three group as SCN lesioned (n:20), sham SCN lesioned (n:20) and intact (n:20). In sham SCN lesioned, animals were exposed to the same surgical procedure with the experimental group except for the lesioned. The animals coming from LD 12: 12 photoperiod were SCN lesioned. The anxiety (open field, elevated plus maze), depression (porsolt) and memory (morris water maze) experiments were performed in all groups in different time points of the day (06:00, 12:00, 18:00 and 24:00). We started the experiment after a week of the SCN lesioned, when surgery wounds healed up completely.

Experimental protocol 3

Intact Rats (n:20)

↓ 1 Week Later

Groups

- 1) 06:00 (n:5)
- 2) 12:00 (n:5)
- 3) 18:00 (n:5)
- 4) 24:00 (n:5)

Applied Tests

Anxiety
Open Field
Elevated Plus Maze

Depression
Porsolt

Learning and Memory
Morris Water Maze

Intact Rats (n:20)

↓ 1 Week Later

Groups

- 1) 06:00 (n:5)
- 2) 12:00 (n:5)
- 3) 18:00 (n:5)
- 4) 24:00 (n:5)

Applied Tests

Anxiety
Open Field
Elevated Plus Maze

Depression
Porsolt

Learning and Memory
Morris Water Maze

Intact Rats (n:20)

↓ 1 Week Later

Groups

- 1) 06:00 (n:5)
- 2) 12:00 (n:5)
- 3) 18:00 (n:5)
- 4) 24:00 (n:5)

Applied Tests

Anxiety
Open Field
Elevated Plus Maze

Depression
Porsolt

Learning and Memory
Morris Water Maze

3.5. Anesthesia

Before surgery, hamsters were anesthetized intraperitoneally with Ketamine (20 mg/kg BW, Sigma Chemical Company, MO, USA) and intraperitoneally with alfazyme (10mg/kg BW, Sigma Chemical Company, MO, USA). Depth of anesthesia was monitored by frequent testing for presence of leg flexion reflexes and active muscle tonus.

3.6. Pinealectomy

Before surgery, the hamsters were anesthetized intraperitoneally with Ketamine (20mg/kg, Sigma Chemical Company, St. Louis, Missouri, USA) and intraperitoneally with pentobarbitol (32.5 mg/kg, Sigma Chemical Company, St. Louis, Missouri, USA). The depth of anesthesia was monitored by the frequent testing of leg reflexes and muscle tonus.

Pinealectomy of hamster was performed according to the method of Hoffmann and Reiter (Hoffman and Reiter, 1965); aspiration was used to control the hemorrhaging. Anesthetized rats were placed in a stereotaxic apparatus to stabilize the head during surgery. After the head was shaved the surgical area was sterilized with 70% ethanol, an incision was made in the scalp. Muscle attachments were removed from the dorsal skull. After drying the skull, an incomplete circular cut was made with a dental drill burr at the λ (lambda) suture and a piece of cranium covering the pineal gland was folded forward anteriorly. The fine-tipped forceps was used to extend into the confluence of the sinuses to grasp and remove the pineal gland. After removal of the pineal gland, the bone flap was replaced and a small square of absorbable gelatin sponge (Gelfoam, Up John, Kalamazoo, MI) was applied to the skull surface to help promote clotting. The scalp was closed with stainless steel surgical clips. After

surgery, the incision was treated with new skin adhesive to prevent any contamination. At the end of the experiment, pinealectomized animals were decapitated and checked for the security of the pinealectomy.



Figure 5. Bregma and lambda regions

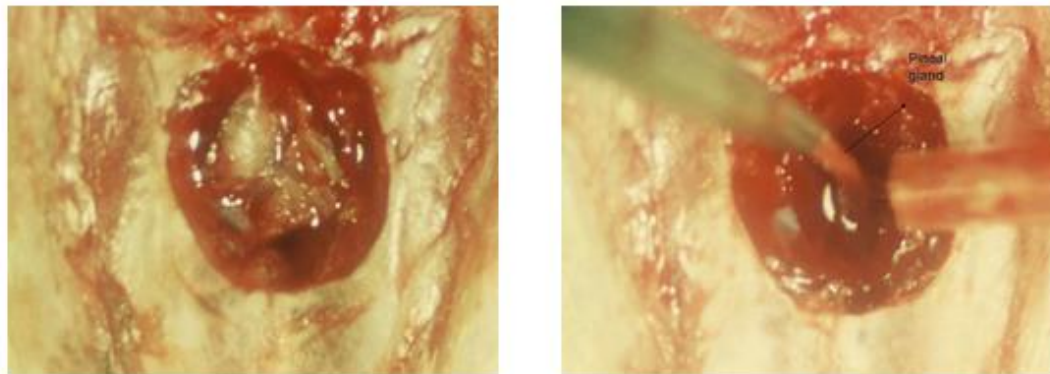


Figure 6. Removal of pineal gland

3.7. Suprachiasmatic nucleus lesion

Before surgery, the rats were anesthetized subcutaneously with Ketamine (20mg/kg, Sigma Chemical Company, St. Louis, Missouri, USA) and intraperitoneally with pentobarbitol (32.5 mg/kg, Sigma Chemical Company, St. Louis, Missouri, USA). The depth of anesthesia was monitored by the frequent testing of leg reflexes and muscle tonus. Anesthetized rats were placed in a stereotaxic apparatus to stabilize the head during surgery. After the head was shaved the surgical

area was sterilized with 70% ethanol, an incision was made in the scalp. Muscle attachments were removed from the skull. The stereotaxic system is based on the flat skull position in which bregma and lambda lie in the same coronal plane so we determined bregma and lambda. After drilling a hole in the skull, an electrode was inserted into the SCN region using stereotaxic coordinates (anterior 0.6mm; lateral from midline 0.1 mm; and ventral 7.8 mm relative to bregma). Lesions were made by current injection (4mA for 10 sec) through a stainless steel wire electrode insulated except at the tip (0.3 mm). The scalp was closed with stainless steel surgical clips. After surgery, the incision was treated with new skin adhesive to prevent any contamination. At the end of the experiment, scn lesions animals were decapitated and checked for the security of the scn lesions.

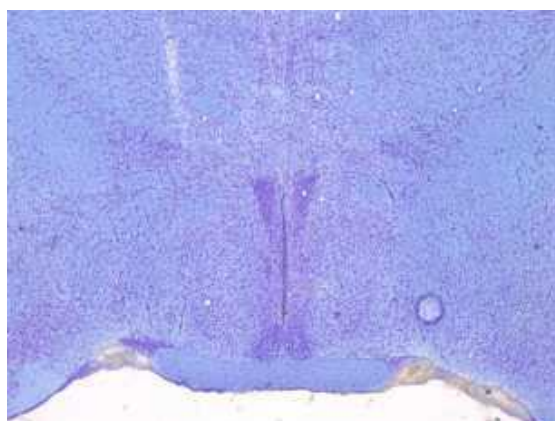
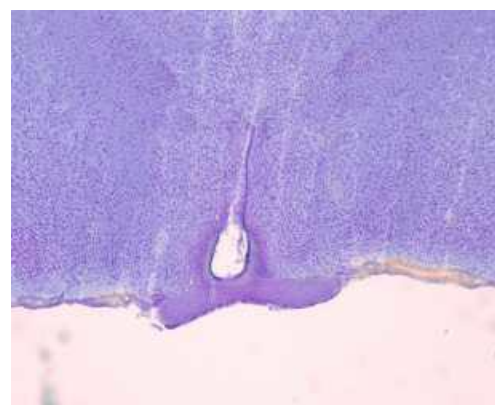


Figure 7.A. Intact Scn



7.B. Scn lesion

3.8. Open Field

Open-field test is taken place in 80 cm×80 cm arena with 40 cm high walls. The open field has been the most widely used test in animal psychology. In this test, an animal (usually a rodent) is introduced into a plain and illuminated arena and its behavior is commonly regarded as a fundamental index of general behavior. In this

experiment a video camera (Gkb CC-28905S, Commat LTD.ŞTİ. Ankara/Turkey) was mounted above the arena, recording behavior into the Ethovision videotracking system (Noldus Ethovision, Version 6, Netherland; Commat LTD.ŞTİ. Ankara/Turkey) that provided avariety of behavioral measures including distance, time in the edge, time in the center, frequency in the edge, frequency in the center, mobility and velocity among the different areas of the arena. All animals were then returned to the breeding and exhibition colonies.

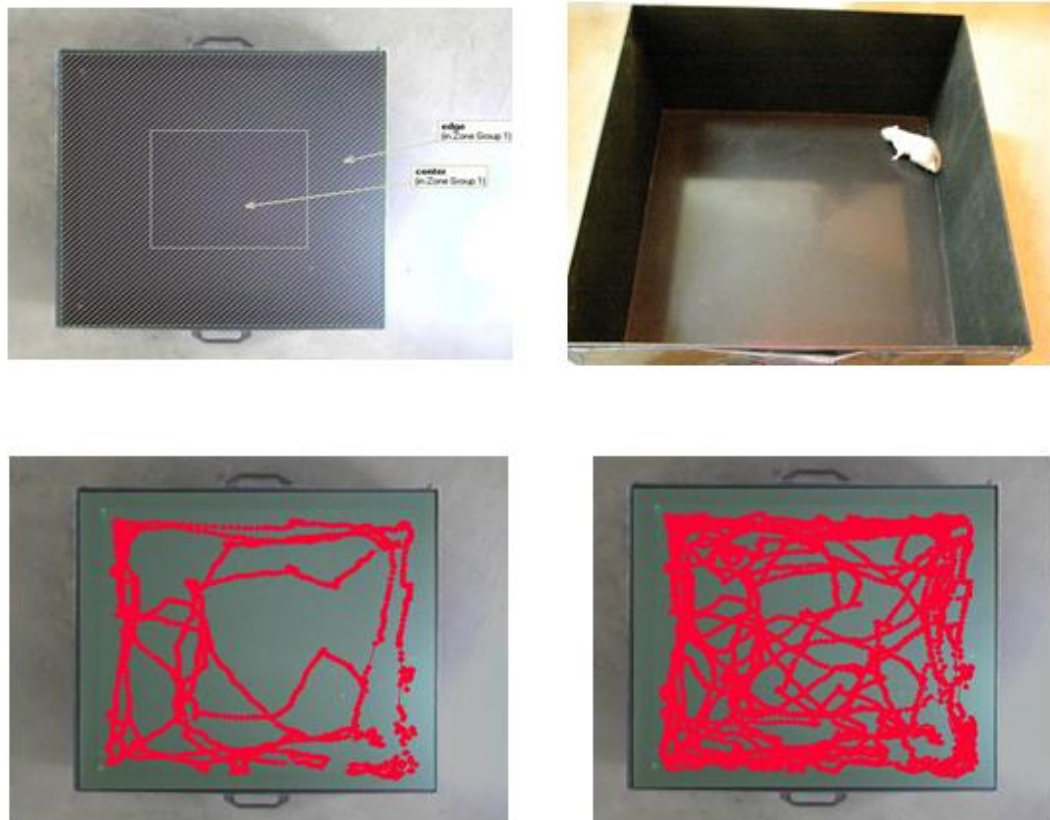


Figure 8. Open field apparatus and Ethovision video tracking system

3.9. Elevated Plus Maze

The elevated plus maze consisted of the two open and two closed 10 cm wide arms in a plus-sign configuration 55 cm off the floor. The closed arms were enclosed by 41 cm tall black Plexiglas. All arms were covered with contact paper to prevent the

animals from sliding off, and all surfaces were wiped with 70% alcohol between animals. Each animal was released into one of the closed arms and allowed to move freely on the maze for a 5-min testing period that was videotaped from above the maze. Animals that fell off the maze into compartments below were placed back on the maze for the remainder of the testing period. An observer uninformed about experimental conditions scored the videotapes with The Observer Software (EthoVision XT) (Noldus Ethovision, Version 6, Netherland; Commat LTD.ŞTİ. Ankara/Turkey) for distance, duration in the open arm, frequency in the open arm, duration in the closed arms, frequency in the closed arms, mobility, and velocity. Animals were considered to have entered an arm when all four paws crossed onto the arm.

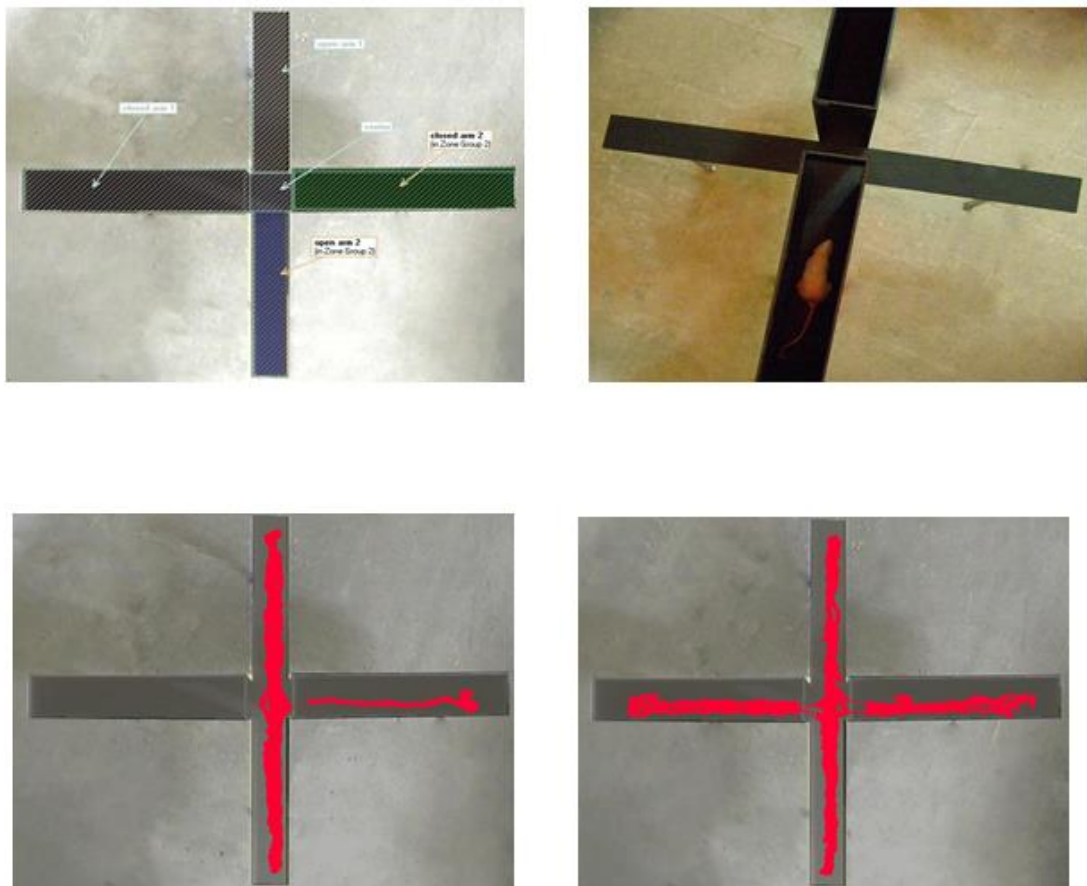


Figure 9. Elevated plus maze and Ethovision video tracking system

3.10. Morris Water Maze

For the spatial memory, the performances of the rats in the Morris water maze were evaluated. The experiments were carried out in a circular, galvanized steel maze (1,5 m in diameter and 60 cm in depth), which was filled with 40 cm deep water kept at 28 °C and rendered opaque by the addition of a non-toxic, water soluble dye. The maze was located in a large quiet test room, surrounded by many visual cues external to the maze (e.g. the experimenter, ceiling lights, rack, pictures, etc.), which were visible from within the pool and could be used by the rats for spatial orientation. Locations of the cues were unchanged throughout the period of testing. A video camera fixed to the ceiling over the center of the maze was used for recording and monitoring movements of the animals. There were the four equally divided quadrants in the pool. In one of the quadrants, a platform (2.0 cm below water surface, 10 cm in diameter) was submerged centrally and fixed in position which was kept constant throughout the acquisition trials. The rats performed the four trials perday for the four consecutive days (16 trials). In the swimming trials, each individual rat was released gently into the water at a chosen quadrant except for the one that contained the hidden platform for facing an extra maze cue. The rat swam and learned how to find the hidden platform within 60 s. The escape latency which is the time elapsed before the rat reached the platform in each trial, is a measure of acquisition of spatial navigation. After reaching, the rat was allowed to stay on the platform for 15 s and was then taken back into the cage. During the inter-trial intervals, animals were kept in a dry home cage for 60 s.

A platform (10 cm diameter) was placed in one of the four maze quadrants (the target quadrant) and submerged 2.0 cm below the water surface. The platform remained in the same quadrant during the entire experiment. The rats were required to find the platform using only distal spatial cues available in the testing room. The cues

were maintained constant throughout the testing. The rats received the four consecutive daily training trials. The video camera recordings were obtained on the fifth day of the experiment. The rat had to swim until it climbed onto the platform submerged underneath the water. The escape platform was kept in the same position relative to the distal cues. The time to reach the platform (latency in seconds), total distance travelled, and time passed in the correct quadrant, entrance frequency to the correct quadrant, and immobility were measured as the indexes of the spatial memory. In this experiment a video camera (Gkb CC-28905S, Commat LTD.ŞTİ. Ankara/Turkey) was mounted above the arena, recording behavior into the Ethovisionvideotracking system (Noldus Ethovision, Version 6, Netherland; Commat LTD.ŞTİ. Ankara/Turkey) that provided avariety of behavioral measures including distance, time in the edge, time in the center, frequency in the edge, frequency in the center, and immobility among the different areas of the arena. All animals were then returned to the breeding and exhibition colonies.

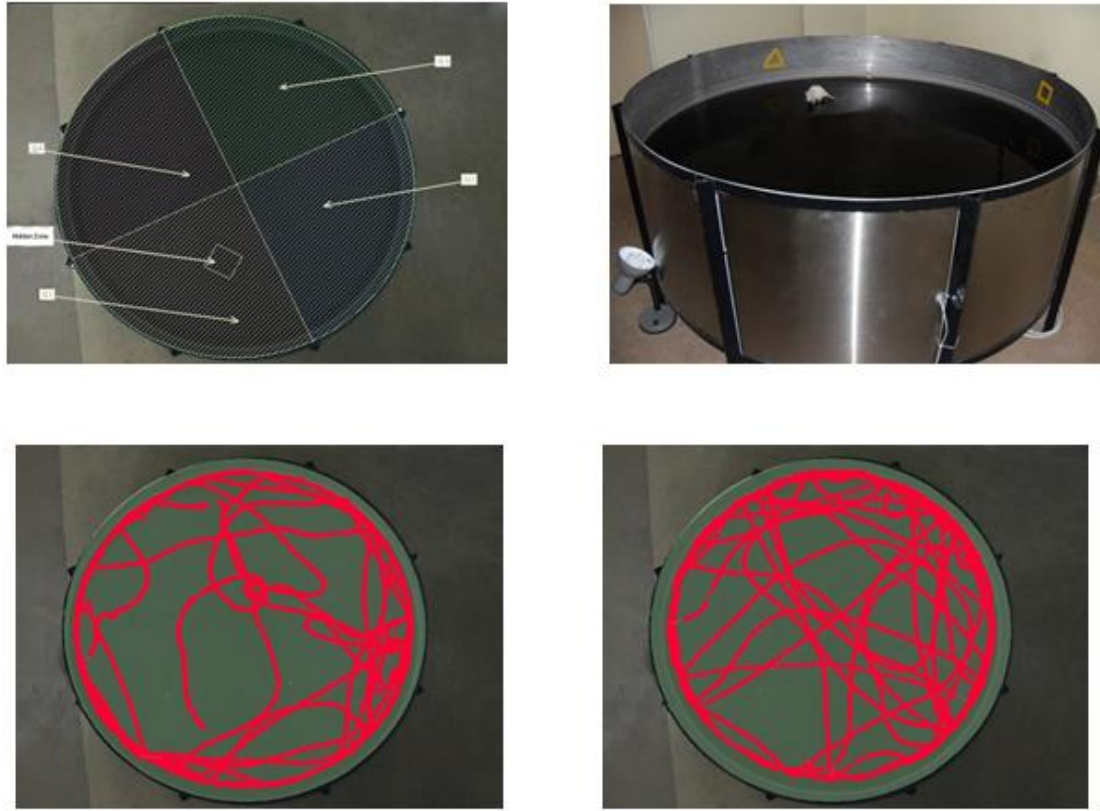


Figure 10. Morris water maze and Ethovision video tracking system

3.11. Forced swim test (Porsolt)

To evaluate depressive- like responses subjects were placed in porsolt which consist of an opaque cylinder tank (24 cm diameter, 53 cm height) which was filled with 17 cm deep water kept at 28 °C. Swimming behavior was recorded on video for 5 minutes. In this experiment a video camera (Gkb CC-28905S, Commat LTD.ŞTİ. Ankara/Turkey) was mounted above the arena, recording behavior into the *Ethovision* videotracking system (Noldus Ethovision, Version 6, Netherland; Commat LTD.ŞTİ. Ankara/Turkey) that provided avariety of behavioral measures including mobility time, mobility frequency, total distance travel, immobility time, rotation, velocity.

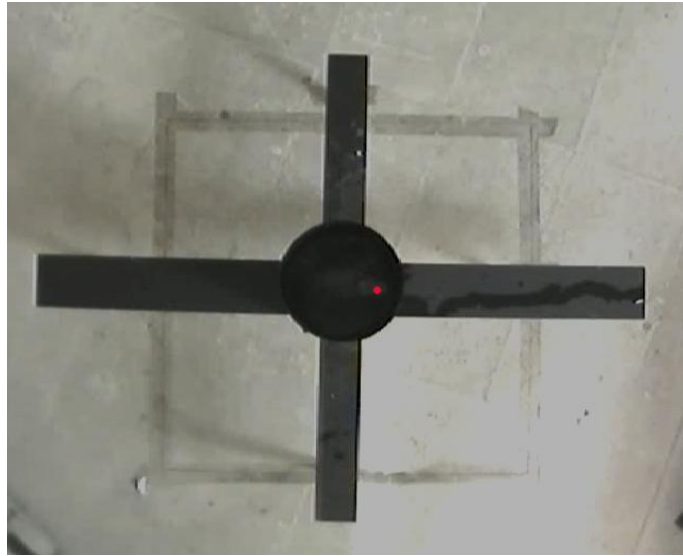


Figure 11. Porsolt Apparatus

3.12. T maze test

T-maze is a maze which has special length and width with 3 sections. There are removable doors at the beginning of the maze and at the end of its sections. These doors are used that hamster are blocked to see the section which have food in it. The floor, walls and doors of the maze are black; other parts are white. Test contains habituation, one-section adaptation, attempt to modify and delayed-response attempts. At the stage of habituation, it is provided that hamster recognize the environment and find the food which is placed to end of the sections, putting the hamster to maze. At one-section adaptation step, it is provided that hamster learn this section, placing the food to only one section. Modifying step also consist of two parts. At the information part, the first step, it is provided that hamster find freely the section with food. At the selection part, the second one, food is placed to section which mice did not enter there before, putting the hamster to the start box just after the information step. This step is continuing until the 75% of hamster find the right section two days in a row. At the delayed-response attempts, final step, the hamster is being waited in other cage, among the information and selection stage of the previous step, during 30,

60 or 90 seconds. This test is aimed to measure the working memory performance of hamsters through measuring the parameters of delayed-response. In this experiment a video camera (Gkb CC-28905S, Commat LTD.ŞTİ. Ankara/Turkey) was mounted above the arena, recording behavior into the *Ethovision* video tracking system (Noldus Ethovision, Version 6, Netherland; Commat LTD.ŞTİ. Ankara/Turkey).



Figure 12. T-Maze

3.13. Statistical Analyses

In the first study, data were analyzed using SPSS (SPSS Statistical Software, SPSS Inc., Los Angeles, CA, USA, Ver. 15.0). Data were analyzed by 2 treatment (pinealectomy and control) X 3 photoperiod (long photoperiod, short photoperiod and normal photoperiod) X 2 sex (female and male) ANOVA analysis with the last factor as a within subject or repeated design. Significant ANOVA results were also tested by

the post hoc test, namely Tukey test which is assumed to be a strong test for comparison of groups that has equal variance and sample size. Values were considered statistically significant at $p \leq 0.05$. Data are presented as MEAN $\pm$ SEM after back transforming from ANOVA results.

In the second study, data were analyzed using SPSS (SPSS Statistical Software, SPSS Inc., Los Angeles, CA, USA, Ver. 15.0). Data were examined by a means of 2 (the presence of treatment: juveniles born from pinelectomized mothers and control (juveniles born from sham-pinelectomized mothers) X 3 photoperiod (the juveniles born from of mothers were subjected to long photoperiod, short photoperiod and normal photoperiod) between ANOVA design. The Post hoc test, Tukey test, was conducted to test significant effects regarding the type of treatment groups. Since each treatment group had its own control (sham) group, comparisons between treatment group and control group for each one was tested by the independent t test. Values were considered statistically significant at $p < 0.05$. Data are presented as MEAN $\pm$ SEM after back transforming from ANOVA results.

In the third study, data were analyzed using SPSS (SPSS Statistical Software, SPSS Inc., Los Angeles, CA, USA, Ver. 15.0). Data were analyzed by 3 (Scn lesions, control (sham) and control (intact)) X 4 (time of the day: 06:00, 12:00, 18:00, and 24:00) ANOVA analysis with the last factor as a within subject or repeated design. Significant ANOVA results were also tested by the post test, namely Tukey test which is assumed to be a strong test for comparison of groups that has equal variance and sample size. Values were considered statistically significant at $p \leq 0.05$. Data are presented as MEAN $\pm$ SEM after back transforming from ANOVA results.

4. RESULTS

4.1. RESULTS OF FIRST STUDY

4.1.1. Open Field Measurements

4.1.1.1. Total distance travelled on the open field (TDT)

The main effect of the photoperiod was significant on the total distance travelled in the open field, $F(2,162) = 4.50$, $p = 0.01$. There was very significant effect of pinealectomy, pinealectomized hamsters exhibited more total activity than control in the open field arena $F(1,162) = 12.00$, $p = 0.001$. Female hamster differed significantly from male hamster in the percentage of their total distance travelled on the open field, $F(1,162) = 6.61$, $p = 0.01$. Females ($M = 3989.48$) travelled more distance than males ($M = 3675.57$). This means males were more anxious than females.

On the other hand, there was significant effect of interaction between photoperiod and pinealectomy $F(2,162) = 3.54$, $p = 0.03$. This interaction reflected fact that pinealectomy groups travelled more distance than control groups in long photoperiod but they were almost the same as control groups in normal and short photoperiods (see figure 13.A). This means that both pinealectomy and long photoperiod decreased anxiety.

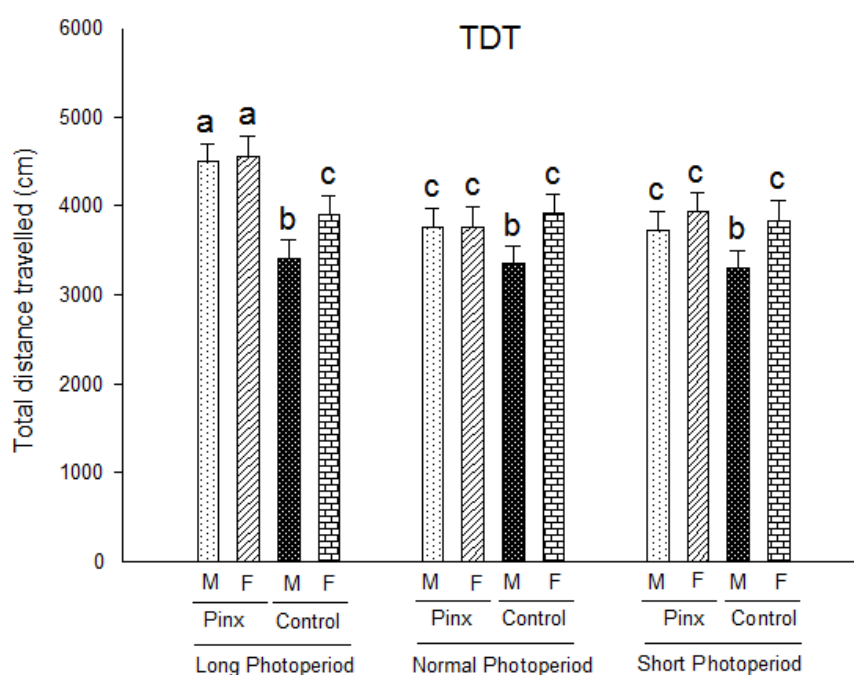


Figure 13.A Mean (S.E.M.) total amount distance travelled (TDT). Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b, c mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.1.1.2. Time spent at the edge of the open field (TSEO)

The main effect of the photoperiod was significant in amount of time spent at the edge of the the open field, $F(2,162) = 4.04$, $p = 0.02$. The percentage of total activity time at the edge of differ according to sex and pinealectomy when assessed at this parameter (sex: $F(1,162) = 5.55$, $p = 0.02$; pinealectomy; $F(1,162) = 4.71$, $p = 0.03$): Males ($M = 4.43$) spent more at the edge of it than females ($M = 4.33$). This indicated that males were more anxious than females. Pinealectomized hamsters ($M = 4.33$) spent

less time than controls ($M=4.43$). This means pinealectomized hamsters were less anxious than controls.

Another significant effect was interaction effect of photoperiod and sex, $F(2,162) = 3.68$, $p=0.03$. This means that males spent more time than females in long and normal photoperiod than males but this trend was absent in the short photoperiod (see Figure 13.B). Males were more anxious than females in long and normal photoperiod but they had the same anxiety as females in short photoperiod. There was a significant effect of interaction between sex and pinealectomy in amount of time spent at the edge of the open field $F(1,162) = 7.10$, $p=0.008$. Pinealectomized males ($M=4.44$) were more anxious than pinealectomized females ($M=4.21$) but in the control condition males and females were similar to each other (see Figure 13.B).

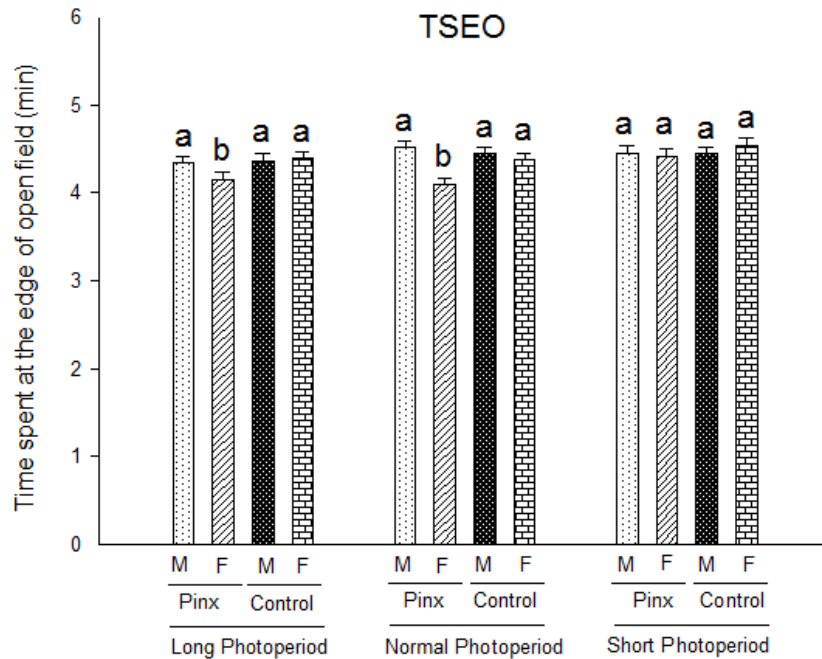


Figure 13.B Mean (S.E.M.) time spent at the edge of the open field (TSEO). The figure explanations are represented in figure 13.A. a, b mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.1.1.3. Time spent at the center of the open field (TSCO)

The main effect of the photoperiod was significant in amount of time spent in the center of the open field, $F(2,162) = 4.06$, $p = 0.02$. The subjects in the long ($M = 0.69$) and normal photoperiod ($M = 0.65$) spent more time than those in the short photoperiod ($M = 0.54$). This means less level of anxiety in the long and normal photoperiod than short photoperiod. Gender exhibited significant differences according to the percentage of total activity time in the center of the open field arena, $F(1,162) = 5.54$, $p = 0.02$. Males ($M = 0.57$) spent less time than females ($M = 0.68$). This means males were more anxious than females.

Another significant effect was interaction effect of photoperiod and sex $F(2,162) = 3.66, p = 0.03$. Males were more anxious than females in long and normal photoperiod but they had the same anxiety as females in short photoperiod. In addition to this, there was very significant effect of interaction between sex and pinealectomy according to the amount of time spent in the center of the open field, $F(1,162) = 7.10, p = 0.008$. Pinealectomized males ($M = 0.56$) were more anxious than pinealectomized females ($M = 0.78$) because they spent less time at the center of open field than females but in the control condition males and females were similar to each other (see Figure 13.C).

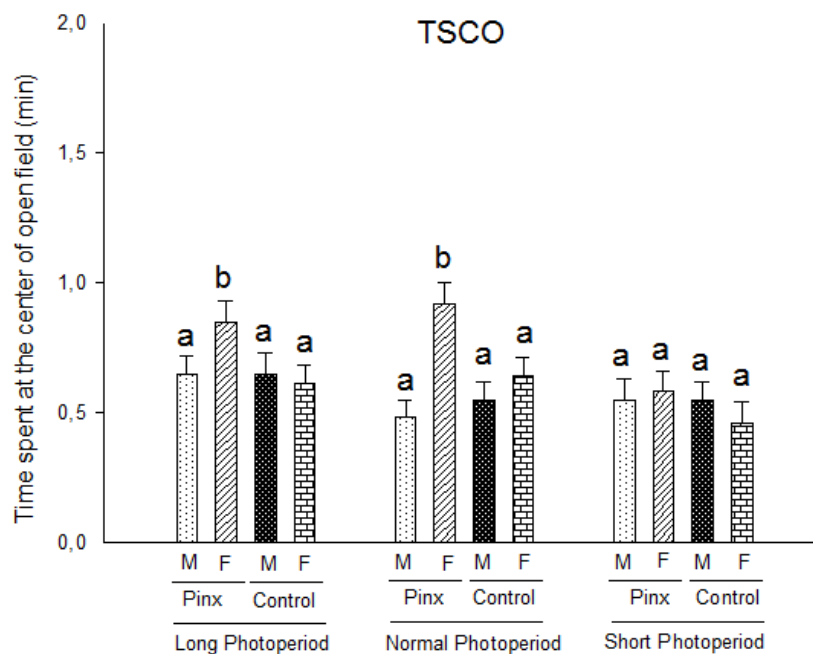


Figure 13.C Mean (S.E.M.) time spent at the center of the open field (TSCO). The figure explanations are represented in figure 13.A. a, b mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.1.4. Total entry to the center of the open field (EFCO)

No main effects related to photoperiod or pinealectomy or interactions thereof were evident in the total entry to the center of the open field.

However, female hamsters were significantly different from male hamsters in the total entry to the center of the open field, $F(1,162) = 4.46$, $p = 0.04$. In short, females ($M = 19.99$) entered more frequently than males ($M = 17.64$). This means that males were more anxious than females.

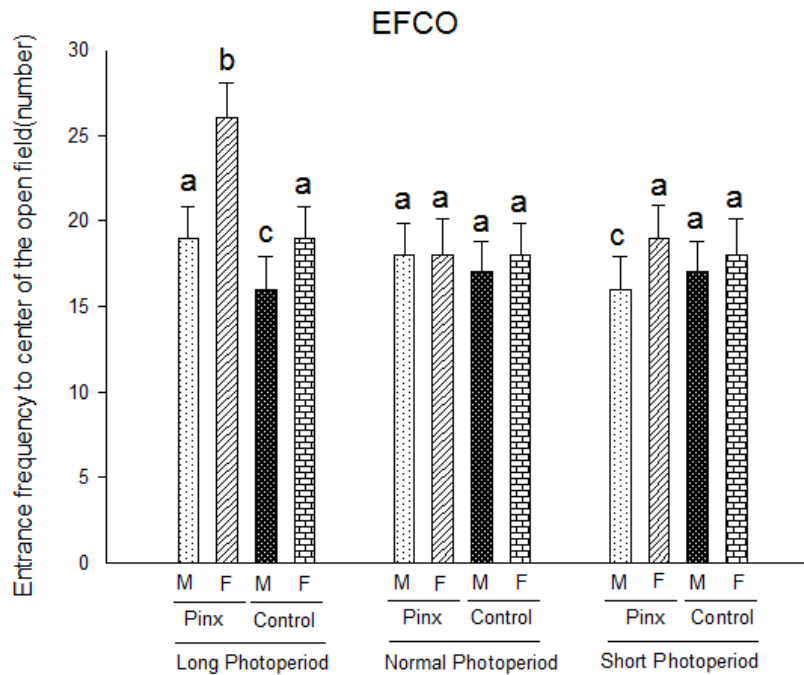


Figure 13.D Mean (S.E.M.) the frequency of entries to the center in the open field (EFCO). The figure explanations are represented in figure 13.A. a, b, c mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.1.5. Mobility in open field (MT)

The main effect of the photoperiod was significant on the mobility, $F(2,162) = 7.11$, $p = 0.001$. The subjects in the long photoperiod ($M = 0.10$) were more mobile than

those in the normal ($M=0.01$) and short photoperiod ($M =0.02$). This means the low level of anxiety in long photoperiod than short and normal photoperiod. There were significant differences between pinealectomized hamsters and control hamsters, even pinealectomized hamsters ($M=0.08$) were more mobile than control ones ($M=0.02$), $F(1,162) =8.79$, $p=0.003$.

Another significant effect was interaction effect of photoperiod and sex, $F(2,162) =6.15$, $p=0.003$. Males were more mobile than females in the long photoperiod but this trend was not significant in short and normal photoperiod (see Figure 13.E). In addition to this interaction, the association of pinealectomy and sex created significant impact on mobility, $F(1,162) =4.02$, $p=0.05$. This means that pinealectomized males ($M=0.11$) were less anxious than pinealectomized females ($M=0.04$) because they were more mobile than females but in the control condition males and females were similar to each other (see Figure 13.E). An interaction effect between the photoperiod and pinealectomy was also significant, $F(2,162) =5.84$, $p=0.004$. The pinealectomized subjects in the long photoperiod were more mobile than those in control but this trend was not significant for the normal and short photoperiod. This means the pinealectomized subjects in the long photoperiod were less anxious than those in the short and normal photoperiod. The interaction among pinealectomy, sex, and treatment was significant, $F(2, 162) =6.55$, $p=0.002$. This reflected that males were less anxious in the long and pinealectomy condition than females (see Figure 13.E).

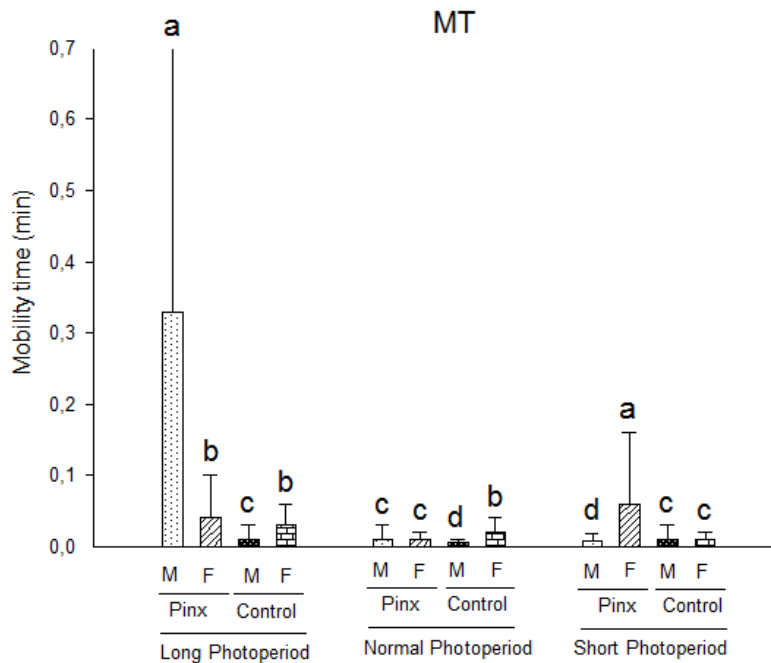


Figure 13.E Mean (S.E.M.) the mobility of the subjects in the open field (MT). The figure explanations are represented in figure 13.A. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p>0.05$)

4.1.1.6. Velocity in open field (VEL)

The main effect of the photoperiod was significant on the velocity in the open field, $F(2,162) = 5.13$, $p = 0.001$. The subjects in the long photoperiod ($M = 825.92$) were faster than those in the normal ($M = 742.56$) and short photoperiod ($M = 741.95$). Gender exhibited significant differences according to the amount of velocity in the open field arena, female ($M = 799.53$) were faster than male hamsters ($M = 740.75$), $F(1,162) = 5.69$, $p = 0.01$. This means that males were more anxious than males. There was very significant effect of pinealectomy, pinealectomized hamsters ($M = 814.46$) were faster than controls ($M = 725.82$), $F(1,162) = 12.69$, $p = 0.0001$. An interaction effect between the photoperiod and pinealectomy was also significant, $F(2,162) = 4.12$,

$p=0.02$. This means that pinealectomized subjects were faster than controls in the long and short photoperiods but in the normal one they were similar to each other.

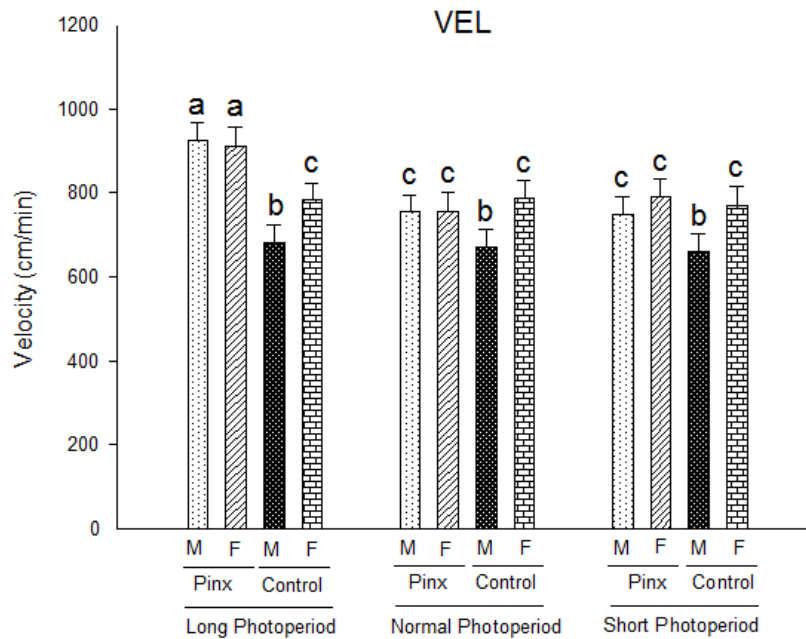


Figure 13.F Mean (S.E.M.) the velocity of the subjects in the open field (VEL).The figure explanations are represented in figure 13.A. a, b, c mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.1.1.7. The Summary of open field results

Long photoperiod had an effect which decrease anxiety of subjects. Subjects who were exposed to long and normal photoperiod spent less time than subjects who were exposed to short photoperiod at the edge of the open field. Process of the pinealectomy decreased anxiety of subjects. Female spent less time than male at the edge of the open field.

4.1.2. Elevated Arm Maze Measurements

4.1.2.1. Total distance travelled on the elevated arm maze (TDT)

The main effect of the sex was significant on the total distance travelled, $F(1,160) = 11.28$, $p = 0.001$. Females ($M=2334.71$) travelled more distance than males ($M=2118.01$). This means males were more anxious than females. The main effect of the treatment was significant on the total distance travelled, $F(1,160) = 14.98$, $p=0.0001$. Pinealectomized subjects ($M=2351.23$) travelled more distance than controls ($M = 2101.49$). There was an interaction effect between photoperiod and sex, $F(2, 60) = 4.34$, $p=0.02$. This reflected that females travelled more distance than males in the long and normal photoperiod but this trend was not significant in the short photoperiod. This means pinealectomized females were the least anxious of all other groups.

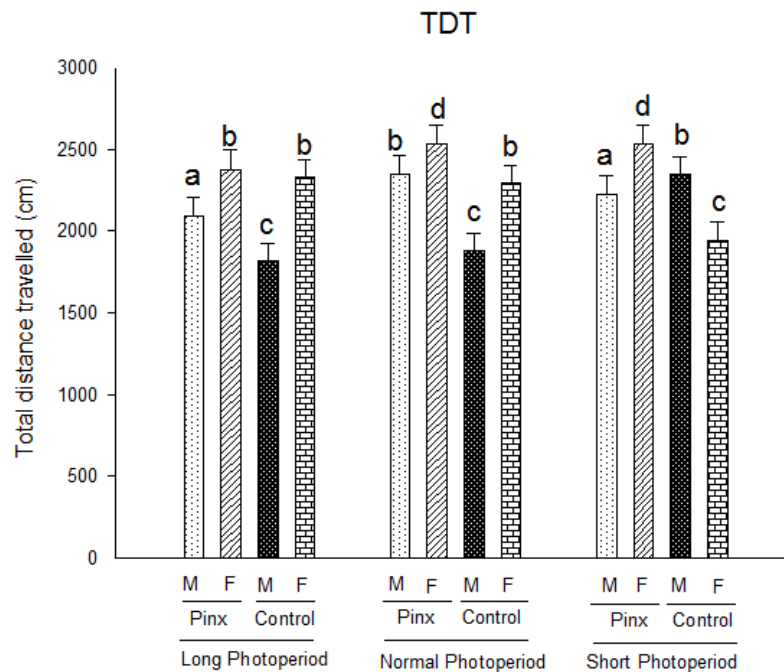


Figure 14.A Mean (S.E.M.) total amount distance travelled (TDT). Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$)

4.1.2.2. Time spent in open arms (TSOA)

An interaction effect between photoperiod and sex was significant on the time spent in open arms, $F(2, 60) = 3.75$, $p = 0.03$. Females spent less time than males in the long and short photoperiod but females spent more time than males in the normal photoperiod (see Figure 14.B). This also means that long and short photoperiod increased the anxiety level of females but these conditions did not change the anxiety level of males.

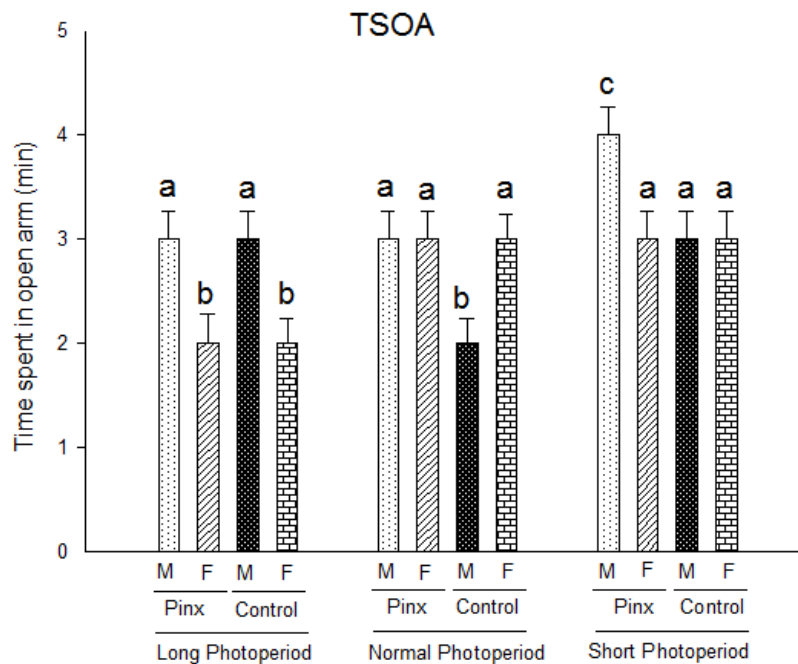


Figure 14.B Mean (S.E.M.) time spent in open arms (TSOA). The figure explanations are represented in figure 14.A. a, b, c mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.2.3. Time spent in closed arms (TSCA)

There was an interaction effect between photoperiod and sex on the time spent in closed arms, $F(2, 60) = 3.87$, $p = 0.02$. Females spent more time than males in the long and short photoperiod but females spent less time than males in the normal photoperiod (see Figure 14.C). This means long and short photoperiod increased the anxiety level of females but normal photoperiod decreased the anxiety level of males.

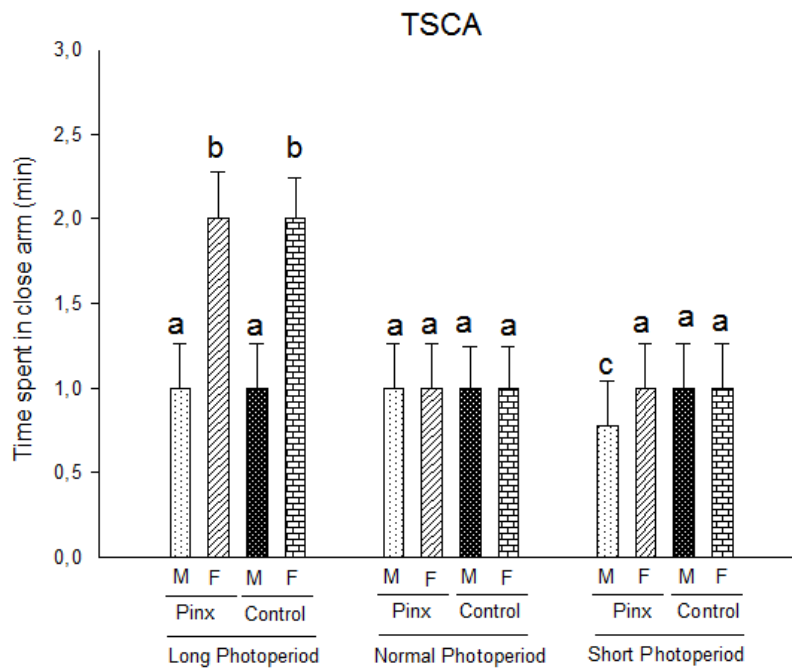


Figure 14.C Mean (S.E.M.) time spent in close arms (TSCA). The figure explanations are represented in figure 14.A. a, b, c mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.2.4. Total entry to closed arms (EFCA)

There was a significant effect of sex on the total entry to closed arms, $F(1,160) = 22.32$, $p = 0.0001$. Females ($M = 4.66$) entered more frequently than males ($M = 3.02$). This means that females were more anxious than males in this measure. An interaction effect between sex and photoperiod was also significant, $F(2,160) = 8.23$, $p = 0.0001$. Females entered more frequently than males in the long and short photoperiod but females entered less frequently than males in the normal photoperiod (see Figure 14.D). This means long and short photoperiod increased the anxiety level of females but normal photoperiod decreased the anxiety level of males. In addition, the interaction effect among photoperiod, sex, and treatment was significant.

Pinealectomized females in the long photoperiod were the most anxious of all other conditions (see Figure 14.D).

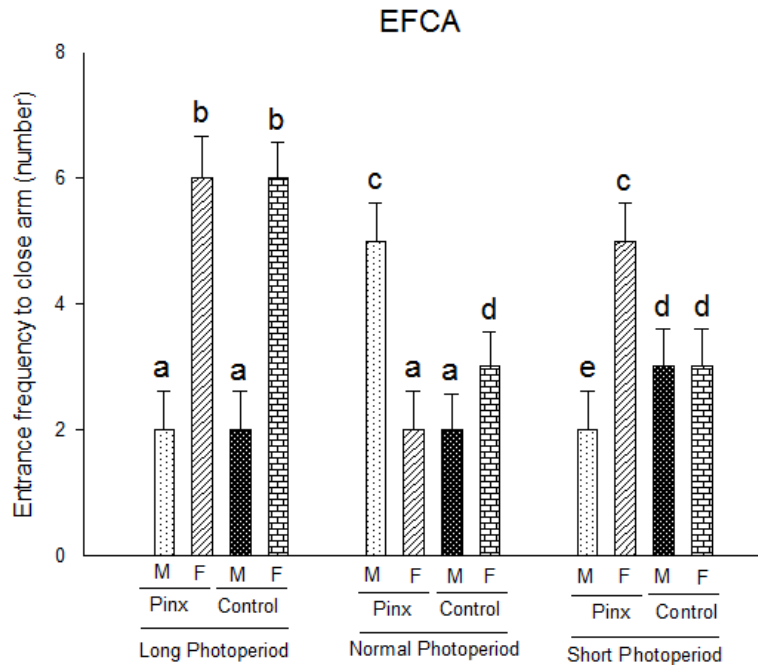


Figure 14.D Mean (S.E.M.) the frequency of entrance to close arms (EFCA). The figure explanations are represented in figure 14.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.2.5. Mobility in elevated plus maze (MT)

The main effect of the photoperiod was significant on the mobility, $F(2,160) = 4.74$, $p = 0.01$. The subjects in the long and short photoperiod were more mobile than those in the normal photoperiod. The main effect of the treatment was also significant on the mobility, $F(1,160) = 7.10$, $p = 0.009$. Pinealectomized subjects were more mobile than control ones. In other words, pinealectomized subjects were less anxious than control ones. An interaction effect between photoperiod and treatment was significant, $F(2,160) = 3.52$, $p = 0.03$. Pinealectomized subjects were more mobile than controls in

the both long and short photoperiod but this trend was not significant in the normal photoperiod (see Figure 14.E).

An interaction effect between photoperiod and sex was significant, $F(2,160) = 8.92$, $p = 0.001$. Males were more mobile than females in the long photoperiod but females were more mobile than males in the short and normal photoperiod (see Figure 14.E). Moreover, the interaction effect among photoperiod, sex, and treatment was significant, $F(2,160) = 10.87$, $p = 0.0001$. Pinealectomized males in the long photoperiod were the most mobile of all groups.

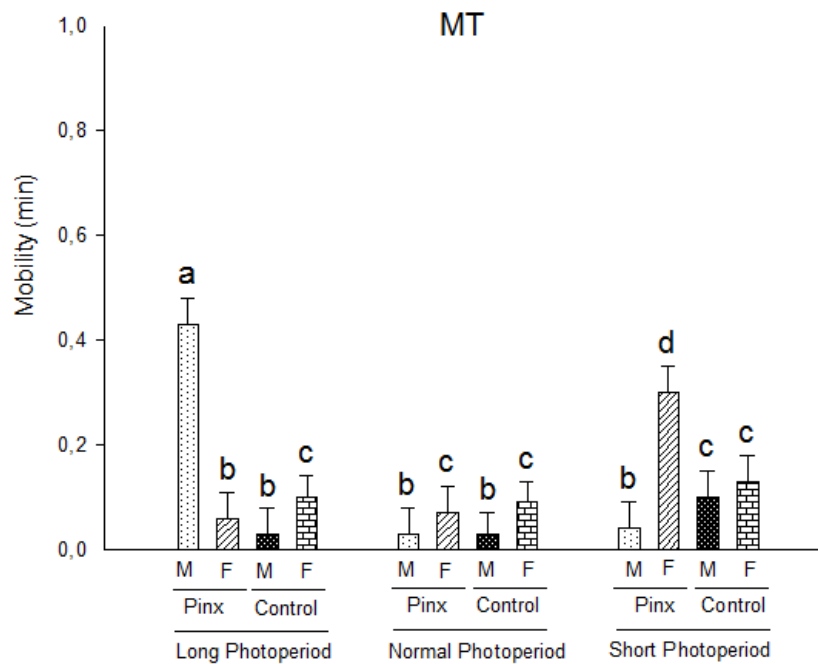


Figure 14.E Mean (S.E.M.) mobility time in elevated plus maze (MT). The figure explanations are represented in figure 14.A. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.2.6. Velocity in elevated plus maze (VEL)

There was a significant effect of photoperiod on velocity, $F(2, 160) = 5.91$, $p = 0.003$. The subjects in the short ($M = 456.82$) and normal photoperiod ($M = 454.73$) were faster than those in the long photoperiod ($M = 404.82$). No significant effects related to the measurement time $F(3, 14) = 1.48$, $p = 0.26$ or pinealectomy $F(1, 16) = 0.28$, $p = 0.61$ or interaction thereof $F(3, 14) = 1.15$, $p = 0.36$ were evident in terms of the velocity of rats in elevated maze.

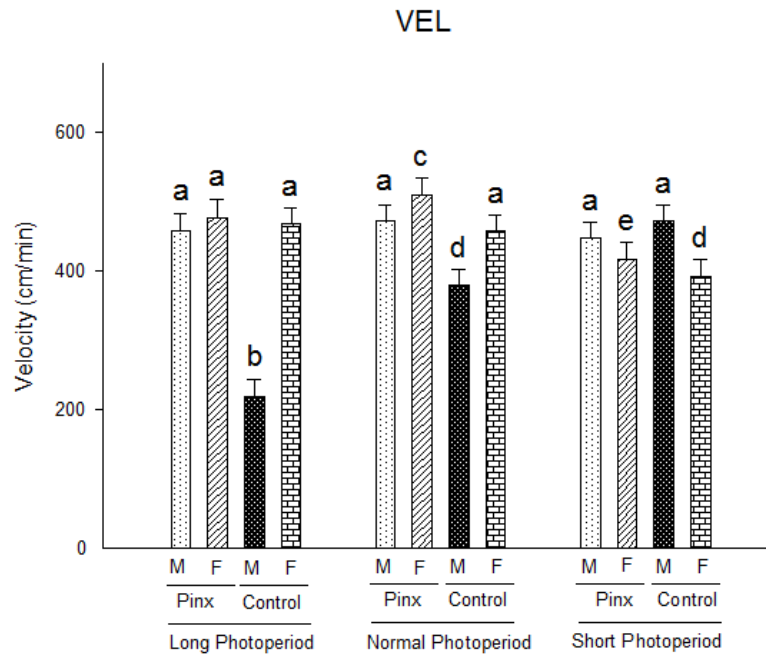


Figure 14.F Mean (S.E.M.) velocity in elevated plus maze (VEL). The figure explanations are represented in figure 14.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.2.7. The Summary of the Elevated Plus Maze Results

There are interaction effect between photoperiod and sex on the time spent in open arms. Process of pinealectomy and sex affect total distance travelled on the elevated plus maze. Especially, pinealectomized female travelled more distance than

all groups. This means that, pinealectomized females were the least anxious of all other groups. The subjects were high mobility and velocity in long photoperiod than other periods. This means that subjects in long photoperiod were the least anxious of all other photoperiods.

4.1.3. Forced Swim Test (Porsolt) Measurements

4.1.3.1. Total distance travelled on the porsolt (TDT)

The main effect of the photoperiod was significant on the total distance travelled on porsolt, $F(2,160) = 3.11$, $p = 0.05$. The subjects in the long photoperiod ($M = 2265.55$) travelled more distance than those in normal photoperiod ($M = 1980.00$). This means that the subjects in the long photoperiod were less depressive than those in normal photoperiod. There was significant effect of sex, $F(1,160) = 8.40$, $p = 0.004$. Males ($M = 1990.75$) travelled less distance than females ($M = 2265.15$). This means that males were more depressive than females. An interaction effect between the photoperiod and sex was significant, $F(1,160) = 5.47$, $p = 0.02$. In the control condition males ($M = 1819.29$) travelled less distance than females ($M = 2319.38$), whereas in pinealectomy condition they were the same in total distance ($M_{\text{Males}} = 2162.21$, $M_{\text{Females}} = 2210.93$). This means that pinealectomy decreased the depression in males.

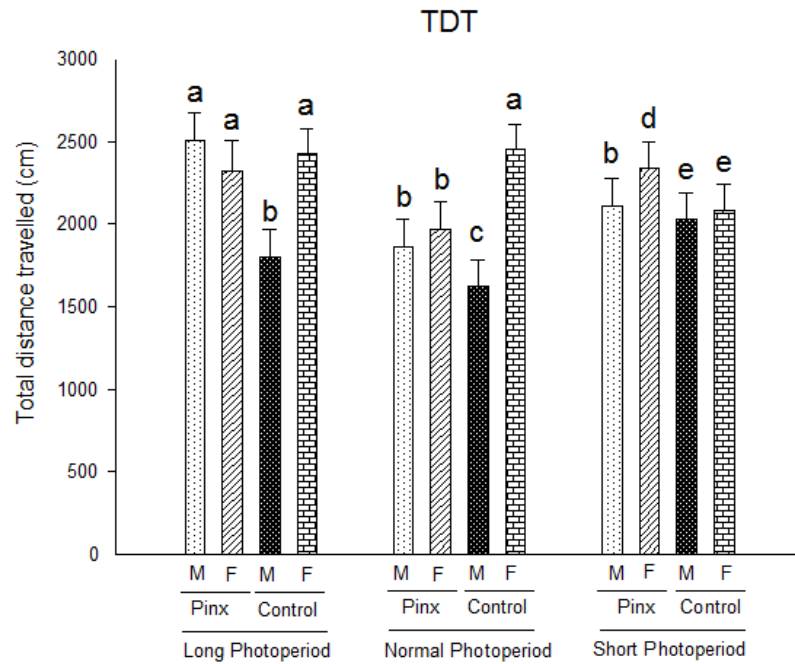


Figure 15.A Mean (S.E.M.) total amount distance travelled (TDT). Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.3.2. Immobility Duration (IT)

The main effect of the sex was significant in the terms of immobility duration in porsolt, $F(1,162) = 5.54$, $p = 0.02$. An interaction effect between the photoperiod and sex was significant, $F(2,160) = 3.31$, $p = 0.03$. There was significant effect of interaction between photoperiod and pinealectomy according to immobility duration $F(2,160) = 3.62$, $p = 0.03$. Moreover, there was also significant effect of

interaction between sex and pinealectomy, $F(1,160) = 19.77$, $p = 0.0001$.

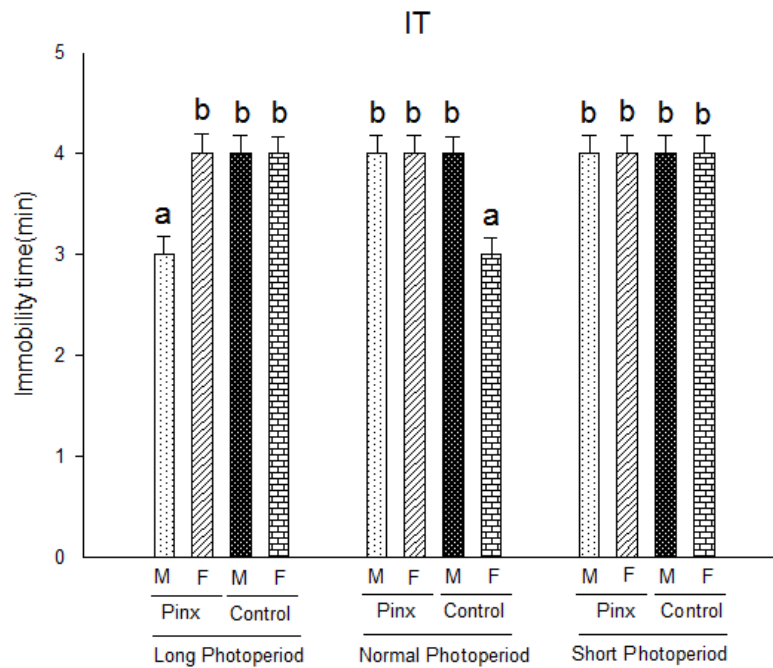


Figure 15.B Mean (S.E.M.) immobility duration in porsolt. The figure explanations are represented in figure 15.A. a, b mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.3.3. Mobility duration (MT)

The main effect of the photoperiod was significant in the terms of mobility duration in porsolt, $F(2,160) = 3.66$, $p = 0.03$. The subjects in the short photoperiod ($M = 0.57$) were more mobile than those in the long ($M = 0.48$) and normal photoperiod ($M = 0.39$). This means that the subjects in the short photoperiod were less depressive than those in the long and normal photoperiod. There were significant effect of pinealectomy, $F(1,160) = 7.27$, $p = 0.008$. Pinealectomized subjects ($M = 0.56$) were more mobile than controls ($M = 0.41$). Pinealectomy decreased depression. An interaction effect between the photoperiod and pinealectomy was significant, $F(2,160) = 3.02$, $p = 0.05$. Pinealectomized subjects ($M_{\text{long}} = 0.59$ and $M_{\text{short}} = 0.70$) were more

mobile than controls in the long (M=0.37) and short (M=0.44) photoperiod but they were the same in the normal photoperiod. There was significant effect of interaction between sex and pinealectomy according to mobility duration $F(1,160) = 13.13$, $p = 0.0001$. Pinealectomized males (M=0.61) were more mobile than pinealectomized females (M=0.51) but control males (M=0.26) were less mobile than control females (M=0.56). This means that pinealectomy decreased depression in males but did not affect it in females.

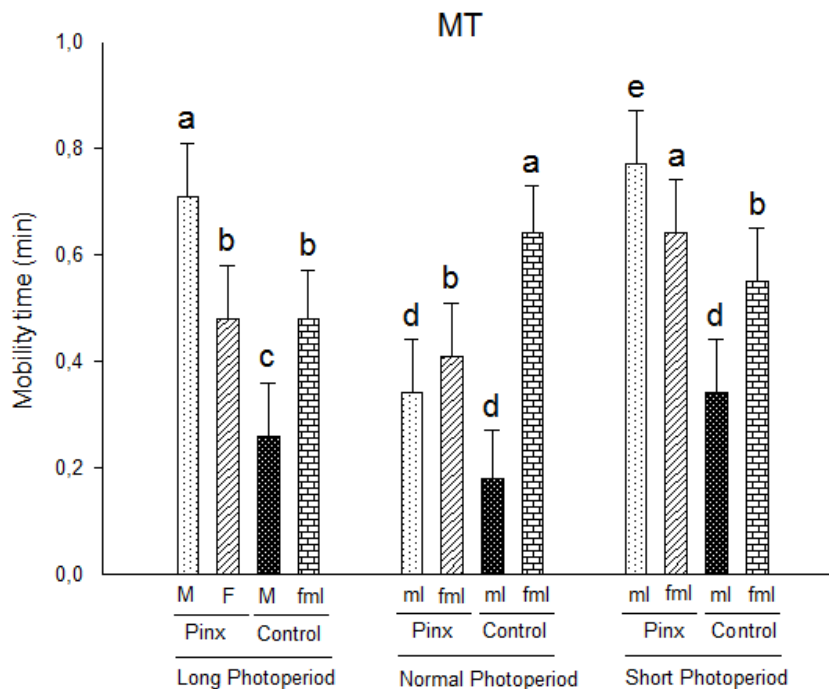


Figure 15.C Mean (S.E.M.) mobility duration in porsolt. The figure explanations are represented in figure 15.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.3.4. Mobility frequency (MF)

There were significant effect of pinealectomy, $F(1,160) = 6.78$, $p = 0.01$. Pinealectomized subjects (M=439.11) had more mobility frequency than controls (M=333.78). Pinealectomy decreased depression. An interaction effect between the

sex and pinealectomy was significant, $F(1,160) = 11.243$, $p = 0.001$. Pinealectomized males ($M = 470.95$) had more mobility frequency than pinealectomized females ($M = 407.26$) but control males ($M = 230.02$) had less mobility frequency than control females ($M = 437.53$). This means that pinealectomy decreased depression in males but did not affect it in females.

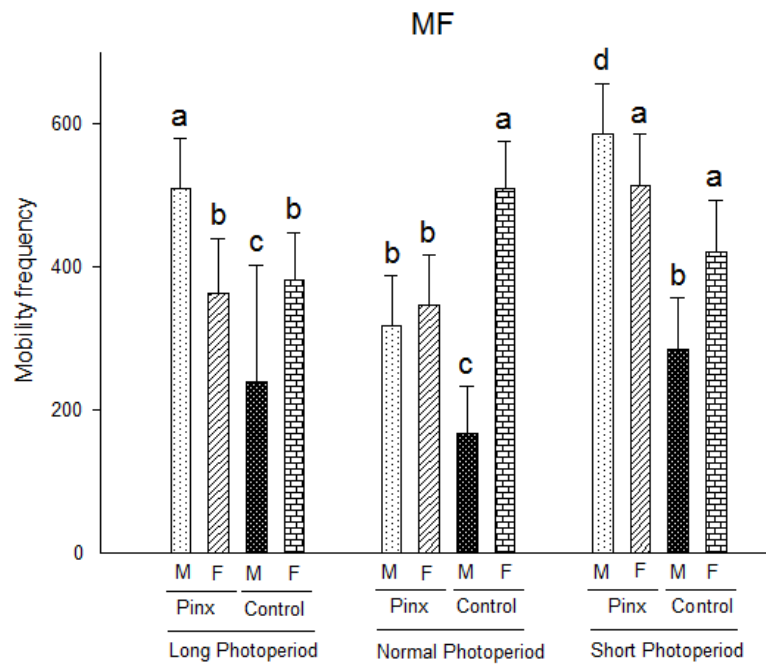


Figure 15.D Mean (S.E.M.) the frequency of mobilite in porsolt. The columns are explained figure 15.A. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.3.5. The summary of porsolt results

The subjects in the short photoperiod were more mobile than those in the long and normal photoperiod. This showed that the subjects in the short photoperiod had power struggle so they were less depressive than those in the long and normal photoperiod. Process of pinealectomy increases mobility of subjects. This situation indicates that depression level of pinealectomized subjects were less.

4.1.4. T -Maze Measurements

4.1.4.1. Total distance travelled on the t-maze (TDT)

The main effect of the sex was significant on the total distance travelled $F(1,156) = 11.23$, $p = 0.001$. Males ($M = 245.38$) travelled more distance than females ($M = 204.01$). Males learnt slower than females. There was significant effect of photoperiod, $F(2,156) = 6.27$, $p = 0.001$. The subjects in the short photoperiod ($M = 254.13$) travelled more distance than those in the long ($M = 200.47$) and normal ($M = 219.47$) photoperiod, with the last two being not significantly different from each other. The subjects in the short photoperiod had more difficulty in learning than those in the long and normal photoperiod.

An interaction effect between the photoperiod and sex was significant, $F(2,156) = 18.28$, $p = 0.0001$. Males travelled less distance than females in the long photoperiod; however, males travelled more distance than females in both short and normal photoperiod (see Figure 16 A). This means that males learnt faster than females in the long photoperiod; however, males learnt slower than females in both short and normal photoperiod.

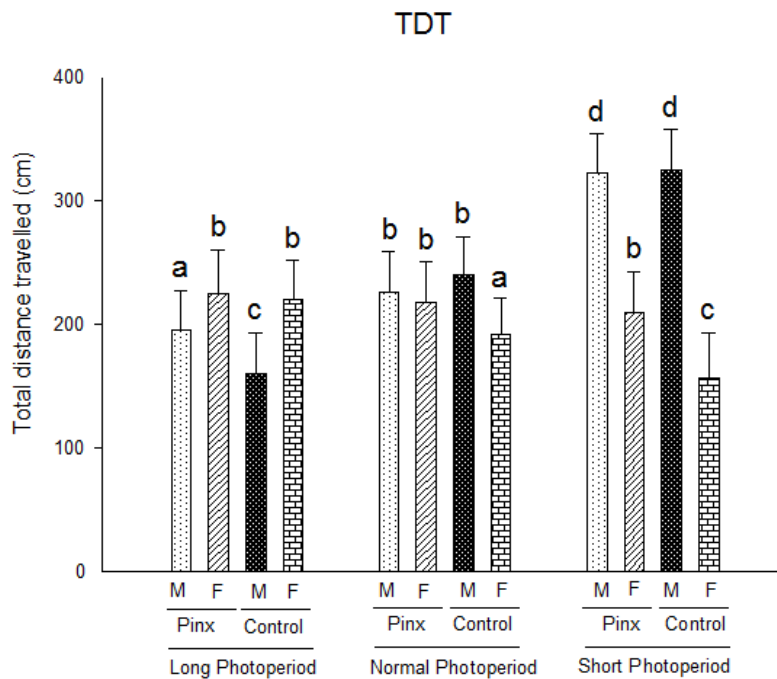


Figure 16.A Mean (S.E.M.) total amount distance travelled (TDT). Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.4.2. Total time spent for finding award (TSFA)

The main effect of the sex was significant on the total time spent for finding award, $F(1,156) = 37.32$, $p = 0.0001$. Males ($M = 245.38$) spent more time to find an award than females ($M = 204.01$). Males learnt slower than females. There was significant effect of photoperiod, $F(2,156) = 14.9$, $p = 0.0001$. The subjects in the short photoperiod ($M = 254.14$) spent more time than those in the short ($M = 219.47$) and normal photoperiod ($M = 200.48$), with the last two being not significantly different from each other. The subjects in the short photoperiod learnt slower than those in the

long and normal photoperiod. An interaction effect between the photoperiod and sex was significant, $F(2,156) = 34.90$, $p = 0.0001$. Males were the slowest learner of all groups in the short photoperiod (see Figure 16.B). There was significant effect of interaction between sex and pinealectomy according to total time spent for finding award, $F(1,156) = 6.22$, $p = 0.01$. Males in contrast to females were not affected by pinealectomy (see Figure 16.B).

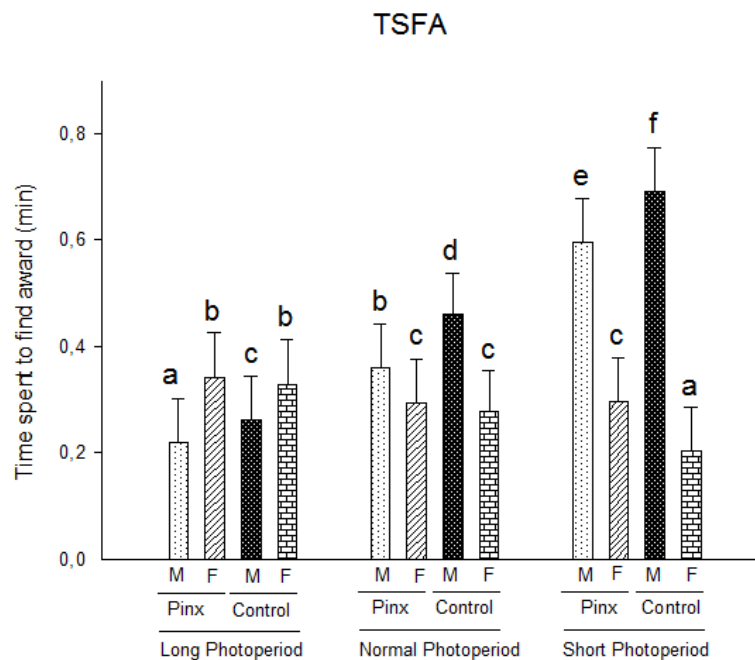


Figure 16.B Mean (S.E.M.) the total time spent for finding award (TSFA). The columns are explained Figure 16.A. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.4.3. Time spent at the decision zone of the T-maze (TSD)

The main effect of the sex was significant on the total time spent at the decision zone of T-maze, $F(1,156) = 35.29$, $p = 0.0001$. There was significant effect of photoperiod $F(2,156) = 19.51$, $p = 0.001$. An interaction effect between the photoperiod and sex was significant, $F(2,156) = 37.66$, $p = 0.0001$. There was significant effect of

interaction between sex and measurement according to total time spent at the decision zone, $F(3,154) = 6.48$, $p = 0.0001$. Moreover, an interaction effect between the photoperiod and measurement was significant, $F(3,155) = 6.10$, $p = 0.0001$. There was significant effect of interaction between sex and measurement according to total time spent at the decision zone, $F(3,154) = 6.48$, $p = 0.0001$. An interaction effect between the sex, measurement and pinealectomy was significant, $F(3,154) = 3.66$, $p = 0.01$. There was significant effect of interaction between measurement, photoperiod and pinealectomy, $F(6,308) = 3.08$, $p = 0.006$. There was significant effect of interaction between measurement, photoperiod and sex, $F(3,308) = 2.61$, $p = 0.02$. There was also significance on the interaction among measurement, photoperiod, sex and pinealectomy, $F(6,308) = 2.21$, $p = 0.04$.

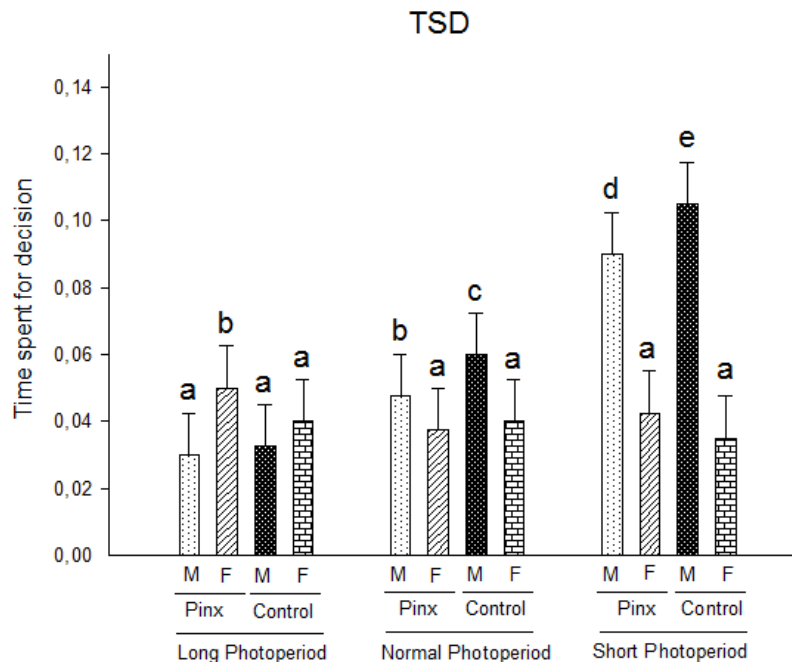


Figure 16.C Mean (S.E.M.) the total time spent at the decision zone of T-maze (TPD). The figure explanations are represented in figure 16.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.4.4. Mobility in T-maze (MT)

The main effect of the photoperiod was significant on the mobility, $F(2,156) = 3.78$, $p = 0.03$. The subjects in the long photoperiod ($M = 0.01$) were more mobile than those in the normal photoperiod ($M = 0.004$). An interaction effect between the photoperiod and pinealectomy was significant, $F(2,156) = 8.04$, $p = 0.0001$. This interaction indicated that the pinealectomized subjects were faster than normal subjects in the long photoperiod. However, in terms of mobility the pinealectomized subjects were the same as normal in the short and normal photoperiod (see figure 16.D).

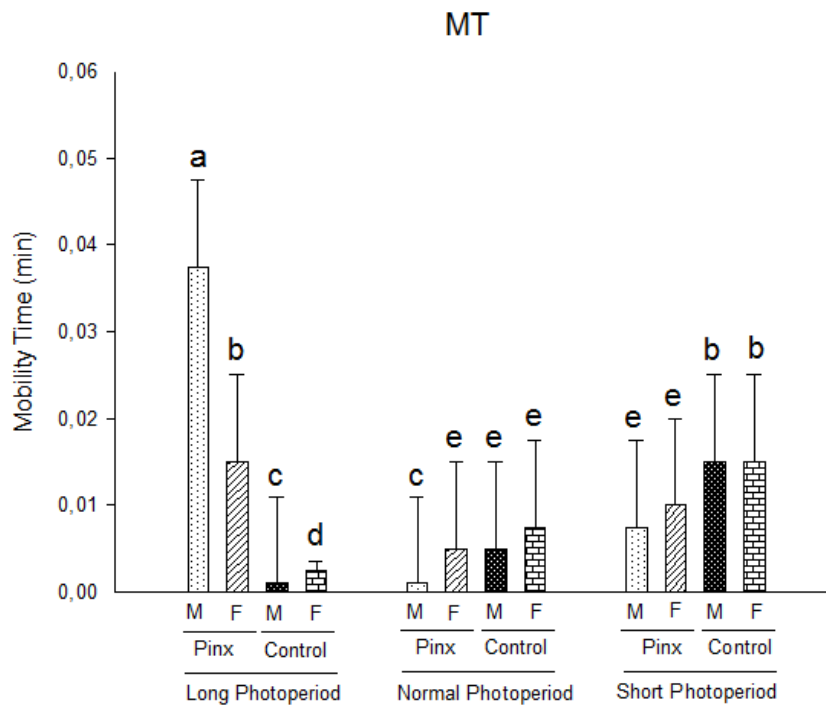


Figure 16.D Mean (S.E.M.) the mobility time in T-Maze. The figure explanations are represented in figure 16.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.1.4.5. Velocity (VEL)

The main effect of the sex was significant on the total distance travelled $F(1,156) = 11.23$, $p = 0.001$. Females ($M = 898.43$) were faster than males ($M = 759.95$). There was a significant effect of photoperiod, $F(2,156) = 9.58$, $p = 0.0001$. The subjects in the long photoperiod ($M = 923.25$) were faster than those in the normal photoperiod ($M = 806.79$) and those in the short photoperiod ($M = 757.53$). An interaction effect between the photoperiod and sex was also significant, $F(2,156) = 7.43$, $p = 0.001$. This indicated that males were faster than females in the long photoperiod; however, females were faster than males in both the normal photoperiod and the short photoperiod (see figure 16.E). In addition, there was a significant interaction effect between sex and pinealectomy on velocity, $F(1,156) = 11.04$, $p = 0.001$. This indicated that females were the same as males in the pinealectomy condition; however, females were faster than males in the control condition (see figure 16.E).

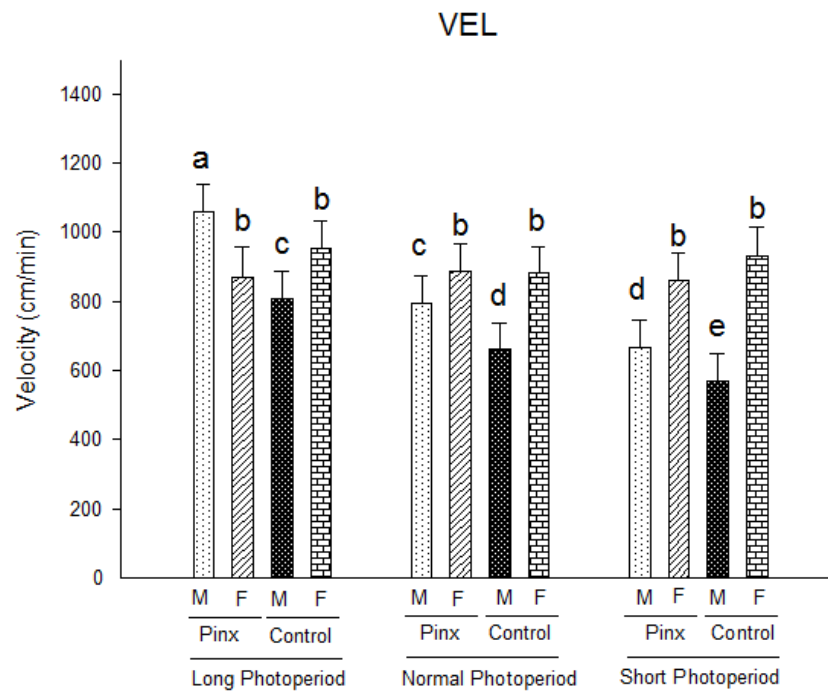


Figure 16.E Mean (S.E.M.) the velocity in T-Maze. The figure explanations are represented in figure 16.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.1.4.6. The summary of T-maze results

Subjects in long and normal photoperiod spent less time for finding award than short photoperiod group and they also travelled less than the subjects in short photoperiod. This means that subjects in normal and long photoperiod learn faster than subjects in short photoperiod.

4.2. RESULTS OF SECOND STUDY

4.2.1. Open Field Measurements

4.2.1.1. Total distance travelled on the open field (TDT)

The main effect of the photoperiod was significant on the total distance travelled in the open field, $F(2,156) = 20.25$, $p = 0.001$. Groups born from mothers who were subjected to long and short photoperiod were more travelled than groups were born from mothers who were subjected to normal photoperiod groups. There was a significant effect of pinealectomy. Hamsters born from pinealectomized mothers ($M = 3154.24$) exhibited less total distance travelled than hamsters were born to control mothers ($M = 3354.11$) in the open field arena $F(1,156) = 3.61$, $p = 0.05$. Female juvenile hamsters ($M = 3593.69$) differed significantly from male juvenile hamsters ($M = 2913.66$) in the percentage of their total distance travelled on the open field $F(1,156) = 42.16$, $p = 0.0001$.

On the other hand, there was a significant effect of interaction between photoperiod and pinealectomy $F(2,156) = 11.99$, $p = 0.0001$. This interaction reflected the fact that hamsters borned from control mothers ($M_{\text{long}} = 3819.36$ and $M_{\text{short}} = 3735.29$) travelled more distance than hamsters borned from pinealectomized mothers ($M_{\text{long}} = 3221.96$ and $M_{\text{short}} = 3196.56$) in long and short photoperiod but hamsters were born from pinealectomized mothers ($M = 3044.21$) travelled more distance than hamsters borned from control mothers ($M = 2504.67$) in normal photoperiod (see figure 17.A). This means that both pinealectomy and photoperiod increased anxiety. There was significant effect of interaction between photoperiod and sex $F(1,156) = 4.67$, $p = 0.03$. Female juvenile hamsters ($M_{\text{long}} = 4124.45$ and $M_{\text{short}} =$

3764.12) in long and short photoperiod differend significantly from male juvenile hamsters ($M_{\text{long}}=2916.88$ and $M_{\text{short}}=3167.73$) in the percentage of their total distance travelled on the open field but they were almost the same as control groups in normal. There was also significant effect of interaction between sex and pinealectomy $F(1,156) = 4.67$, $p=0.03$. Females were borned from pinealectomized mothers ($M=3607.37$) were more anxious than males borned from pinealectomized mothers ($M=2701.11$) because they travelled more in open field than males but in the control condition is similar.

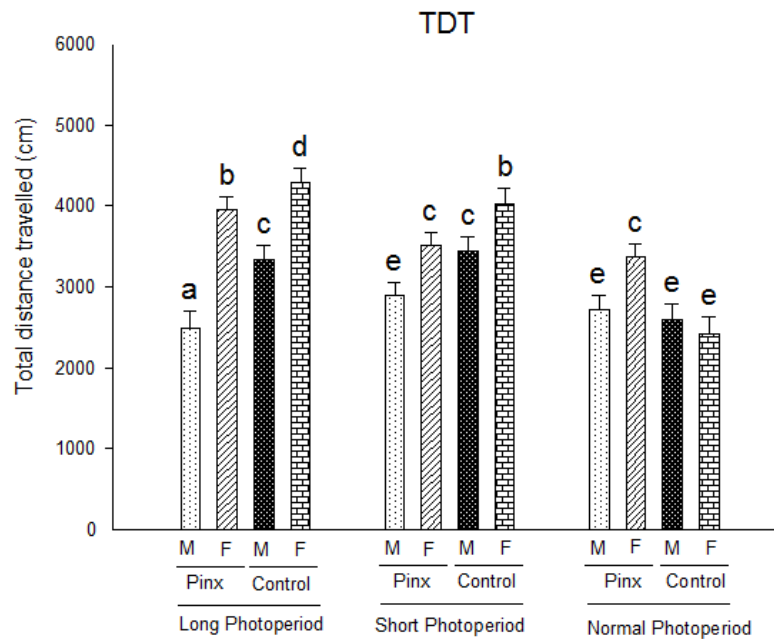


Figure 17.A Mean (S.E.M.) total amount distance travelled (TDT). Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.1.2. Time spent at the center of the open field (TSCO)

The main effect of the pinealectomy was significant in amount of time spent in the center of the the open field, $F(1,156) = 8.60$, $p = 0.004$. Groups borned from pinealectomized mothers ($M = 0.624$) spent less time than groups were born to control mothers ($M = 0.793$) at the center of open field. Another significant effect was interaction effect of photoperiod and pinealectomy $F(2,156) = 8.58$, $p = 0.0001$. Groups borned from pinealectomized mothers ($M_{\text{long}} = 0.41$ and $M_{\text{normal}} = 0.614$) were more anxious than groups borned from control mothers ($M_{\text{long}} = 0.917$ and $M_{\text{normal}} = 0.905$) in long and normal photoperiod but groups borned from pinealectomized mothers ($M = 0.717$) were less anxious groups borned from control mothers ($M = 0.558$) in short photoperiod.

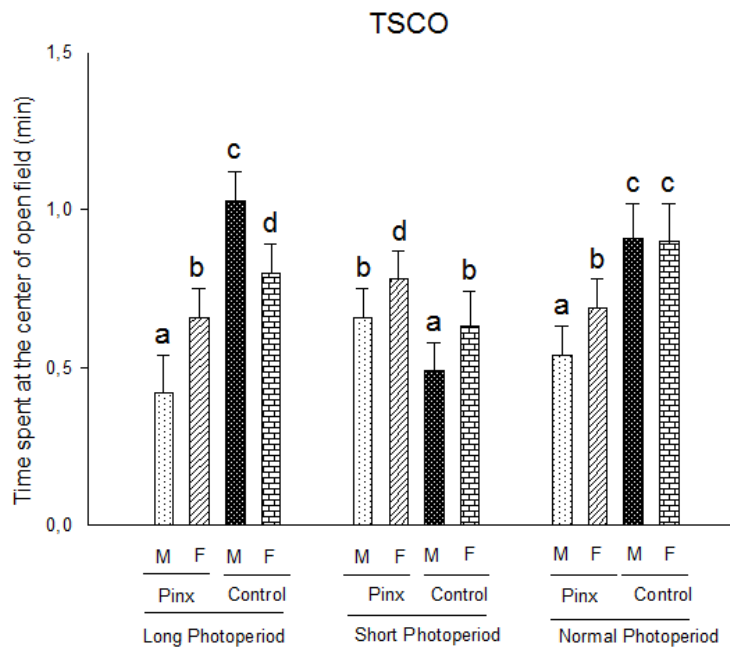


Figure 17.B Mean (S.E.M.) time spent at the center of the open field (TSCO). The figure explanations are represented in figure 17.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.2.1.3. Total entry to the center of the open field (EFCO)

The main effect of the photoperiod was significant in the total entry to the center of the open field, $F(2,156) = 3.51$, $p = 0.03$. Groups were subjected to normal photoperiod ($M = 15.61$) were more anxious than groups were subjected to long ($M = 18.99$) and short photoperiod ($M = 18.03$). Female juvenile hamsters ($M = 21.41$) were significantly different from male juvenile hamsters ($M = 13.67$) in the total entry to the center of the open field, $F(1,156) = 53.59$, $p = 0.0001$.

Females juvenile hamsters borned from mothers subjected to short photoperiod ($M = 22.60$) were less anxious than males juvenile hamsters ($M = 13.45$). There was significant effect of interaction between photoperiod and pinealectomy, $F(2,156) = 10.08$, $p = 0.0001$. Groups borned from pinelectomized mothers were subjected to long photoperiod ($M = 15.49$) entered the center of the open field less frequently than groups borned from control mothers were subjected to long photoperiod ($M = 22.50$) but groups borned from pinelectomized mothers were subjected to normal photoperiod ($M = 17.93$) entered more frequently than groups ($M = 13.28$) borned from control mothers were subjected to normal photoperiod. Groups borned from pinelectomized mothers were subjected to short photoperiod ($M = 18.00$) and groups borned from control mothers were subjected to short photoperiod ($M = 18.06$) are similar each other (See Figure 17.C). An interaction effect between the photoperiod and sex was significant, $F(2,156) = 7.22$, $p = 0.001$. Female juvenile hamsters entered more frequently than male juvenile hamsters in all photoperiod.

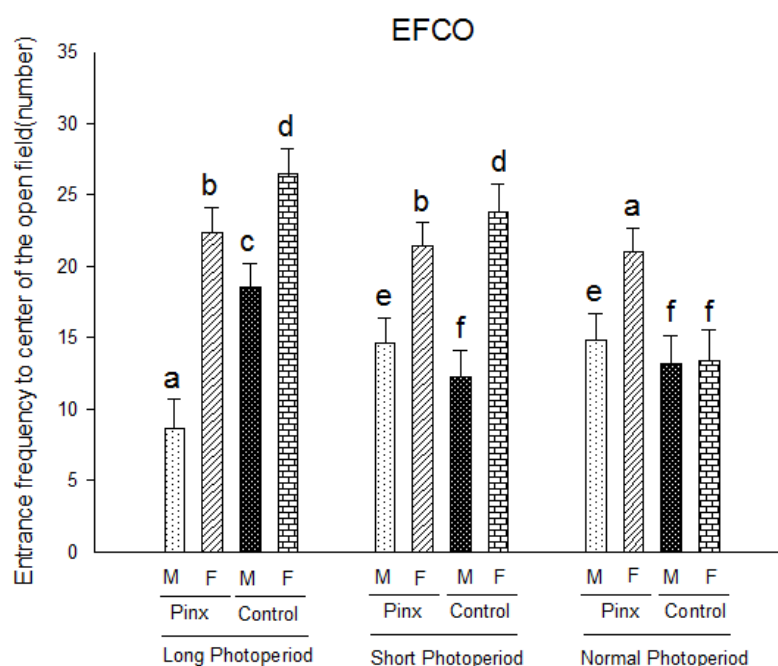


Figure 17.C Mean (S.E.M.) the frequency of enteries to the center in the open field (EFCO). The figure explanations are represented in figure 17.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.1.4. Mobility in Open field (MT)

The main effect of the photoperiod was significant on the mobility, $F(2,156) = 5.87$, $p = 0.004$. The subjects borned from mothers were subjected to short photoperiod ($M = 0.002$) were more mobile than the subjects were born from mothers were subjected to long photoperiod ($M = 0.007$). This means that the juveniles borned from mothers who receive short photoperiod had the low level of anxiety. There were significant differences between juveniles borned to pinealectomized mothers and juveniles were born to control mothers, even juveniles borned to pinealectomized mothers ($M = 0.006$) were more mobile than juveniles borned to control mothers ($M = 0.002$), $F(1,156) = 13.37$, $p = 0.0001$. The main effect of the sex was significant on the mobility $F(1,156)$

=8.69, $p=0.004$. Female juveniles ($M=0.006$) were more mobile than males juveniles ($M=0.002$) in all photoperiod.

Another significant effect was interaction effect of pinealectomy and sex, $F(1,156) = 6.68$, $p=0.01$. This means that males juveniles born to pinealectomized mothers ($M=0.003$) were more anxious than female juveniles were born pinelactomized mothers ($M=0.009$) because they were less mobile than female juveniles but male juveniles ($M=0.002$) born to the control condition and female juveniles ($M=0.002$) born to the control condition were similar to each other (see figure17.D).

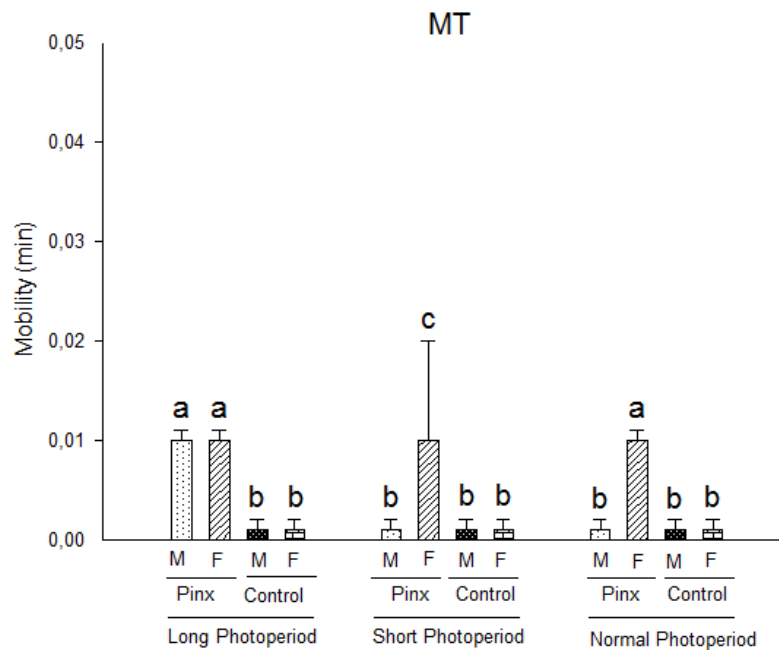


Figure 17.D Mean (S.E.M.) the mobility in open field. The figure explanations are represented in figure 17.A. a, b, c mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.1.4. Velocity in open field (VEL)

The main effect of the photoperiod was significant on the velocity in the open field, $F(2,156) = 20.33$, $p = 0.0001$. The juveniles born to the long photoperiod conditions ($M = 705.39$) and the juveniles born to short photoperiod ($M = 695.03$) were faster than juveniles born to the normal ($M = 555.75$). Gender exhibited significant differences according to the amount of velocity in the open field arena, female juveniles ($M = 720.17$) were faster than male juveniles ($M = 583.94$), $F(1,156) = 42.08$, $p = 0.0001$. There was a very significant effect of pinealectomy, juveniles born from mothers were subjected to control conditions ($M = 671.17$) were faster than juveniles born from pinelectomized mothers ($M = 632.93$) $F(1,156) = 3.58$, $p = 0.05$. An interaction effect between the photoperiod and pinealectomy was also significant, $F(2,156) = 12.04$, $p = 0.0001$. This means that juveniles were born from control mothers were subjected to long and short photoperiod ($M_{\text{long}} = 765.05$ and $M_{\text{short}} = 749.32$) were faster than juveniles born from pinelectomized mothers were subjected to long and short photoperiod ($M_{\text{long}} = 465.73$ and $M_{\text{short}} = 640.74$) but juveniles born from pinelectomized mothers were subjected to normal photoperiod ($M = 610.06$) were faster than juveniles born from control mothers were subjected to same photoperiod ($M = 501.44$). There was a significant effect of interaction between sex and pinealectomy, $F(1,156) = 4.61$, $p = 0.03$. This means that both female juveniles were born from pinelectomized mothers ($M = 722.84$) were faster than male juveniles born from pinelectomized mothers ($M = 541.52$) and female juveniles were born from control mothers ($M = 717.51$) were faster than male juveniles born from control mothers ($M = 626.36$). Another significant effect was interaction effect of photoperiod and sex, $F(2,156) = 7.21$, $p = 0.001$. Female juveniles were faster than male juveniles in all photoperiod.

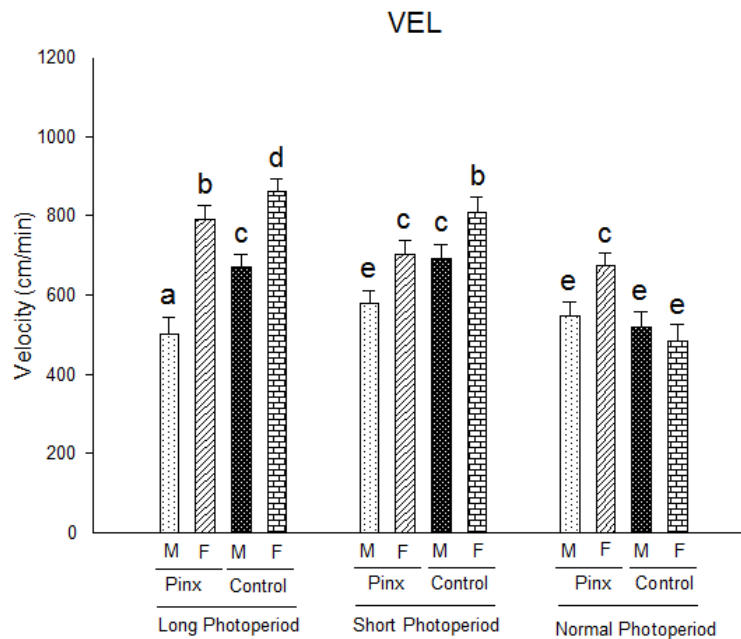


Figure 17.E Mean (S.E.M.).The velocity of the subjects in the open field (VEL). The figure explanations are represented in figure 17.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.2.1.5. The summary of open field results

Effect of long and short photoperiods cause decreasing anxiety level of open field. This effect occurred from parameters which are total entry to the center of open field, mobility and velocity, not time spent at the centre of open field. Pinealectomy decrease anxiety level of subjects. This result was opposite in the first study. Female juvenile hamsters entered more frequently than male juvenile hamsters. This means that female juveniles were less anxious in this test.

4.2.2. Elevated Maze Measurements

4.2.2.1. Total distance travelled on the elevated arm maze (TDT)

The main effect of the sex was significant on the total distance travelled, $F(1,158) = 56.43$, $p = 0.0001$. Female juveniles ($M = 1976.14$) travelled more distance than male juveniles ($M = 1579.72$). The main effect of the treatment was significant on the total distance travelled, $F(1,158) = 4.21$, $p = 0.04$. Juveniles borned from pinealectomized mothers ($M = 1832.05$) travelled more distance than juveniles borned from control mothers ($M = 1723.82$). Another significant effect was photoperiod $F(2,158) = 5.28$, $p = 0.006$. Juveniles borned from mothers were subjected to long photoperiod ($M = 1896.33$) travelled more than both juveniles were born from mothers were subjected to short ($M = 1742.46$) and juveniles borned from mothers were subjected to normal photoperiod ($M = 1695.01$). There was an interaction effect between photoperiod and sex, $F(2,158) = 7.73$, $p = 0.001$. This reflected that female juveniles ($M_{\text{long}} = 2056.10$ and $M_{\text{normal}} = 2036.40$) travelled more distance than male juveniles in the long and normal photoperiod but this trend was not significant in the short photoperiod. There was an interaction effect between photoperiod and pinealectomy $F(2,158) = 13.65$, $p = 0.0001$. This means that juveniles borned from control mothers were subjected to long ($M = 1912.52$) and juveniles borned from control mothers were subjected to short ($M = 1812.87$) travelled more distance than juveniles borned from pinealectomized mothers were subjected to long ($M = 1880.15$) and juveniles borned from pinealectomized mothers were subjected to short ($M = 1672.04$) but this situation was the exact opposite in the normal photoperiod. Another significant effect was interaction effect of pinealectomy and sex, $F(1,158) = 10.28$, $p = 0.002$. Both female juveniles borned from pinealectomized mothers ($M = 2114.87$)

travelled more distance than male juveniles borned from pinealectomized mothers (M=1549.23) and female juveniles borned from control mothers (M=1837.42) travelled more distance than male juveniles borned from control mothers control males (M = 1610.22).

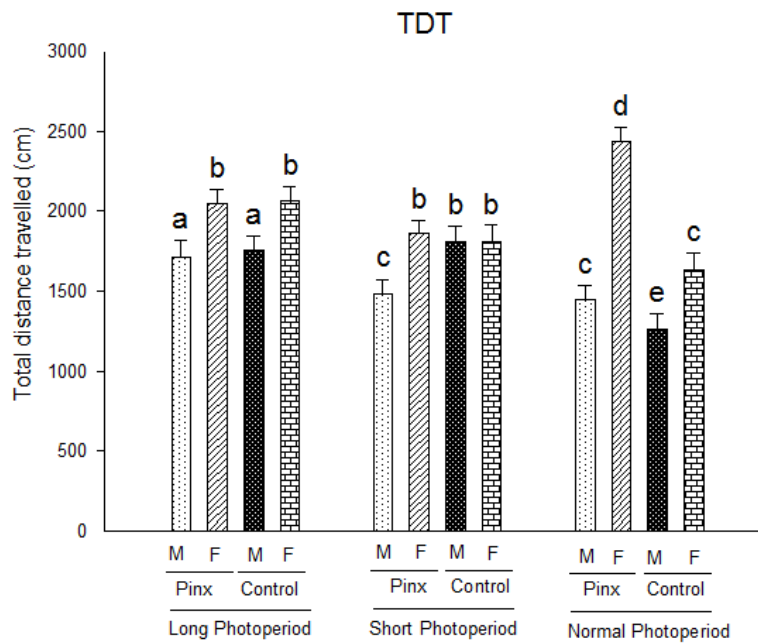


Figure 18.A Mean (S.E.M.) total amount distance travelled (TDT). Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.2.2.2. Time spent in open arms (TSOA)

The main effect of the photoperiod was significant on the time spent in open arms $F(2,158) = 3.56$, $p = 0.03$. This means that increased the anxiety level of juveniles

borned from mothers were subjected to long and short photoperiod because juveniles (M=2.90) borned from mothers were subjected to the normal photoperiod spent more time on the open arms than juveniles borned from mothers were subjected to long and short photoperiod ($M_{\text{long}}=2.67$ and $M_{\text{short}}=2.66$). There was also very significant effect of pinealectomy, $F(1,158)=15.23$, $p=0.0001$. Juveniles borned from pinealectomized mothers (M=2.58) spent less time than juveniles borned from control mothers controls (M=2.90) so birth from mothers had been exposure pinelectomy increased anxiety level of juveniles.

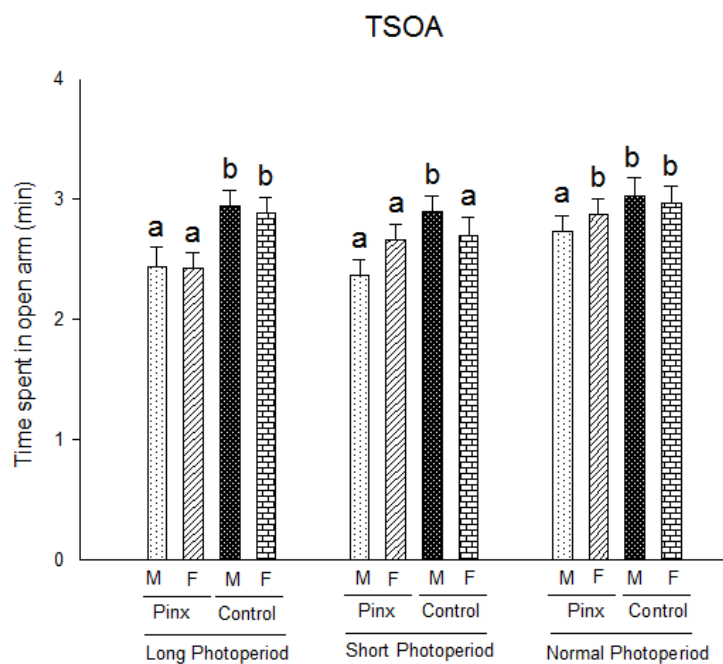


Figure 18.B Mean (S.E.M.) time spent in open arms. The figure explanations are represented in figure 18.A. a, b mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.2.3. Total entry to open arms (EFOA)

There was a significant effect of sex on the total entry to open arms, $F(1,158) = 48.60$, $p = 0.0001$. Female juvenile ($M = 11.53$) entered more frequently than male juveniles ($M = 8.67$). This means that female juveniles were less anxious than male juveniles in this measure. The main effect of the photoperiod was significant on the total entry to open arms $F(2,158) = 11.42$, $p = 0.0001$. To be exposed with long and short photoperiod decreased anxiety level of subjects. Another significant effect was pinealectomy $F(1,158) = 4.44$, $p = 0.04$. An interaction effect between sex and photoperiod was also significant $F(2,158) = 4.76$, $p = 0.01$. Female juveniles borned from mothers were subjected to long photoperiod ($M = 12.97$) and female juveniles borned from mothers were subjected to short photoperiod ($M = 11.05$) entered more frequently than male juveniles borned from mothers were subjected to long photoperiod ($M = 9.17$) and than male juveniles borned from mothers were subjected to short ($M = 9.97$) but female juveniles and male juveniles entered same frequently in the normal photoperiod (see Figure 18.C). This means long and short photoperiod decreased the anxiety level of female juveniles but this trend was not significant in normal photoperiod. In addition, the interaction effect between photoperiod and treatment was significant, $F(2,158) = 5.33$, $p = 0.006$.

Juveniles borned from pinealectomized mothers were less anxious of all other conditions in the normal photoperiod (see Figure 18.C).

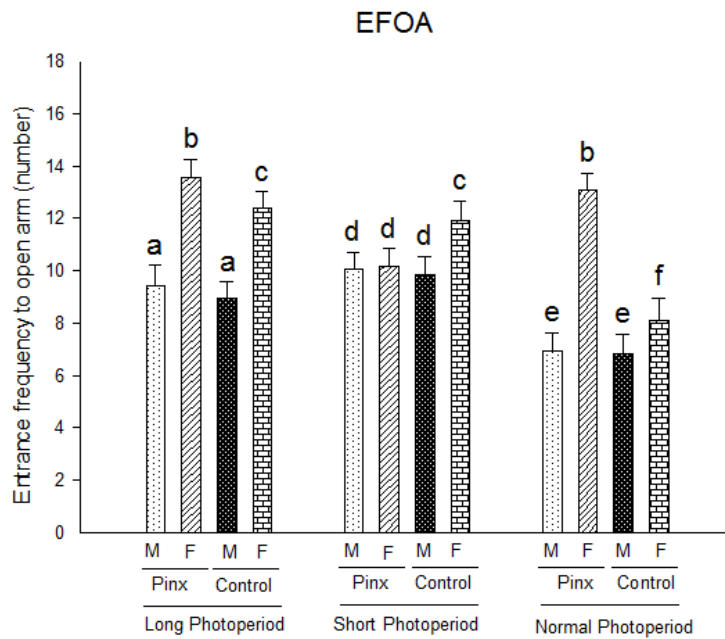


Figure 18.C Mean (S.E.M.) the frequency of entrance to open arms (EFOA). The figure explanations are represented in figure 18.A. a, b, c, d, e, f mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.2.4. Mobility in elevated maze (MT)

The main effect of the photoperiod was significant on the mobility $F(2,158) = 10.76$, $p=0.001$. The juveniles borned from mothers were subjected to normal photoperiod ($M=0.12$) were more mobile than the juveniles borned mothers were subjected to the short photoperiod ($M=0.09$) and it was more mobile than the juveniles borned mothers were subjected to normal photoperiod ($M=0.05$). The effect of the treatment was also significant on the mobility in elevated maze, $F(1,158) = 24.37$, $p=0.0001$. Juveniles ($M=0.12$) borned from pinealectomized mothers were more mobile than juveniles ($M=0.06$) borned from control mothers. In other words, juveniles borned from pinealectomized mothers were less anxious than juveniles borned from control mothers. Another significant effect was sex, $F(1,158) = 7.47$,

$p=0.007$. Female juveniles ($M=0.11$) were more mobile than male juveniles ($M=0.07$) so male juveniles were more anxious than female juveniles. An interaction effect between photoperiod and treatment was significant on the mobility, $F(2,158)=14.56$, $p=0.0001$. Juveniles ($M=0.07$) borned from pinealectomized mothers were subjected to long photoperiod ($M=0.07$) and juveniles ($M=0.07$) borned from pinealectomized mothers were subjected to normal photoperiod ($M=0.20$) were more mobile than juveniles ($M=0.03$) were born from control mothers were subjected to long photoperiod ($M=0.03$) and juveniles ($M=0.04$) borned from control mothers were subjected to normal photoperiod but this trend was not significant in the short photoperiod (see Figure 18.D).

An interaction effect between photoperiod and sex was significant, $F(2,158)=8.28$, $p=0.0001$. Female juveniles ($M=0.18$) borned from mothers were subjected to normal photoperiod were more mobile than male juveniles ($M=0.07$) borned from mothers were subjected to the normal photoperiod but this trend was not significant in the short and long photoperiod (see Figure 18.D). Moreover, the interaction effect between pinealectomy and sex was significant, $F(1,158)=9.84$, $p=0.002$. Female juveniles ($M=0.16$) borned from pinealectomized mothers were the least mobile of all groups so they were the most anxious groups.

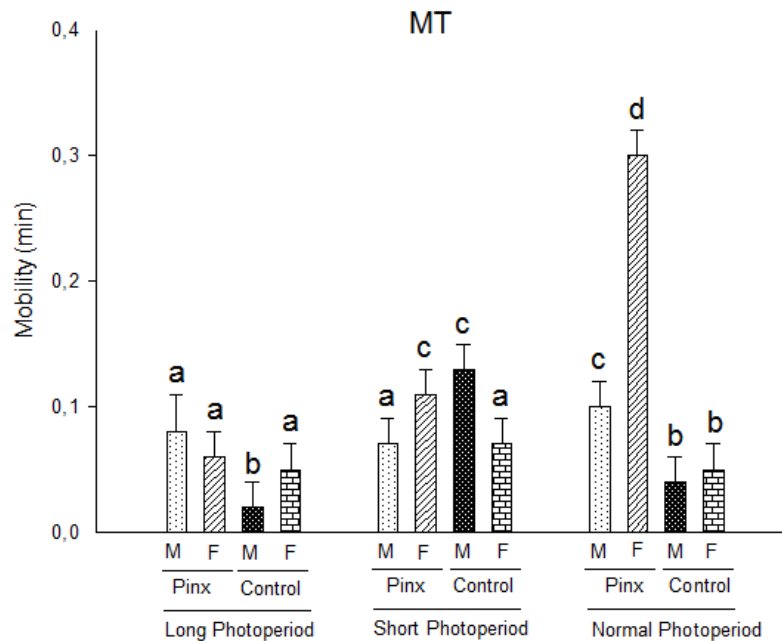


Figure 18.D Mean (S.E.M.) mobility time in elevated plus maze. The columns are explained Figure 18.A. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.2.5. Velocity in elevated maze (VEL)

There was a significant effect of photoperiod on velocity, $F(2,158) = 4.31$, $p = 0.01$. The juveniles ($M = 382.57$) borned from mothers were subjected to long photoperiod were faster than the juveniles ($M = 357.11$) borned from to mothers were subjected to short photoperiod and juveniles ($M = 345.49$) borned from mothers were subjected to normal photoperiod.

There was a significant effect of sex on velocity, $F(1,158) = 57.71$, $p = 0.0001$, female juveniles ($M = 401.58$) were faster than male juveniles ($M = 321.86$) so females had low anxiety level. Another significant effect was treatment $F(1,158) = 4.22$, $p = 0.04$, anxiety level of juveniles who were born from pinealectomized mothers, decreased. An interaction effect between photoperiod and pinealectomy was

significant $F(2,158) = 16.00$, $p = 0.0001$. Juveniles ($M = 376.75$) borned from pinealectomized mothers were subjected to long photoperiod and juveniles ($M = 342.29$) borned from pinealectomized mothers were subjected to short photoperiod were less fast than juveniles ($M = 388.38$) borned from control mothers were subjected to long photoperiod and juveniles ($M = 371.92$) borned from control mothers were subjected to short photoperiod but juveniles ($M = 398.44$) borned to pinealectomized mothers were subjected to normal photoperiod were faster than juveniles ($M = 292.53$) borned from control mothers were subjected to normal photoperiod. This means that to be exposed to long and short photoperiod increased anxiety. An interaction effect between photoperiod and sex was significant $F(2,158) = 8.62$, $p = 0.0001$, females juveniles ($M_{\text{long}} = 413.66$ and $M_{\text{short}} = 375.47$ and $M_{\text{normal}} = 415.59$) borned from mothers were subjected to long, short and normal photoperiods were faster than male juveniles ($M_{\text{long}} = 351.47$ and $M_{\text{short}} = 338.74$ and $M_{\text{normal}} = 275.38$) borned from mothers were subjected to long, short and normal photoperiods. Male juveniles borned from pinealectomized mothers were more anxious than female juveniles borned from pinealectomized mothers because female juveniles ($M = 430.74$) borned from pinealectomized mothers were faster than male juveniles ($M = 314.25$) borned from pinealectomized mother and female juveniles ($M = 372.41$) borned from control mothers were faster than male juveniles ($M = 329.48$) borned from control mothers. An interaction effect between pinealectomy and sex was also significant $F(1,158) = 12.28$, $p = 0.001$.

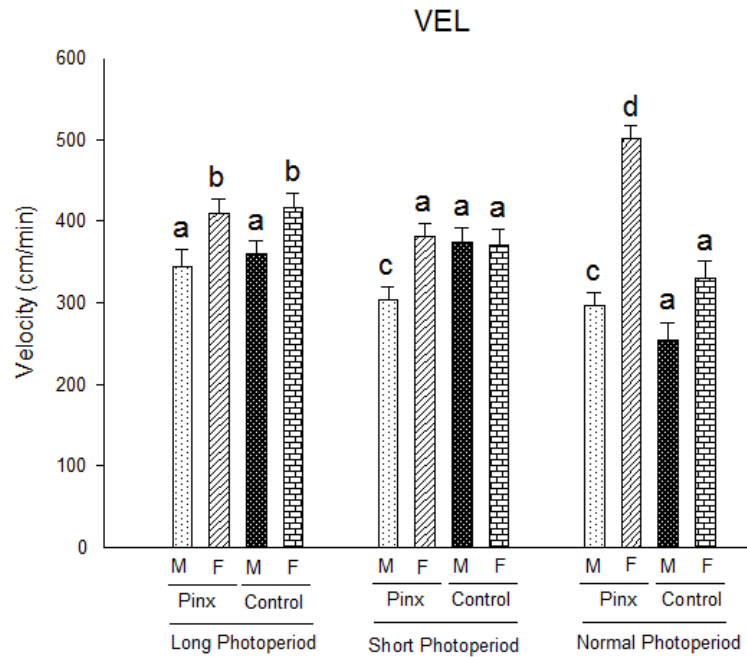


Figure 18.E Mean (S.E.M.) velocity in elevated plus maze. The figure explanations are represented in figure 18.A. a, b, c, d mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.2.2.6. The Summary of Elevated Plus Maze Results

Photoperiod affects anxiety level of juveniles. Juveniles borned from mother who were exposed to long and short photoperiod were more anxious than juveniles borned from mothers who were exposed to normal photoperiod. In addition to this, juveniles borned from pinealectomized mothers who were exposed to long and short photoperiod were more anxious than juveniles were borned from control mothers. Juveniles were borned from pinealectomized mother were more anxious than other juveniles. Female juveniles were more anxious than males. In addition to these, female juveniles borned from mothers were exposed to long and normal photoperiod were anxious than male juveniles in same photoperiods.

4.2.3. Forced Swim Test (Porsolt) Measurements

4.2.3.1. Mobility Duration (MT)

The effects of the photoperiod, sex and pinealectomy were no significant in the terms of mobility duration in porsolt. An interaction effect between the photoperiod and pinealectomy was significant, $F(2,156) = 8.30$, $p = 0.0001$, juveniles borned from pinealectomized mothers were subjected to short and normal photoperiods ($M_{\text{short}} = 0.06$ and $M_{\text{normal}} = 0.06$) spent more time in mobile than juveniles borned from control mothers were subjected to short and normal photoperiods ($M_{\text{short}} = 0.04$ and $M_{\text{normal}} = 0.04$) but this trend was the opposite in long photoperiod. There was significant effect of interaction between sex and pinealectomy according to mobility duration $F(1,156) = 12.67$, $p = 0.0001$. Mobility duration of male juveniles who were borned from pinealectomized mothers decreased. Male juveniles ($M = 0.06$) borned from control mothers spent more time in mobile female juveniles ($M = 0.03$) were born from control mothers. Moreover, an interaction effect between photoperiod and sex was also significant $F(2,156) = 7.56$, $p = 0.001$.

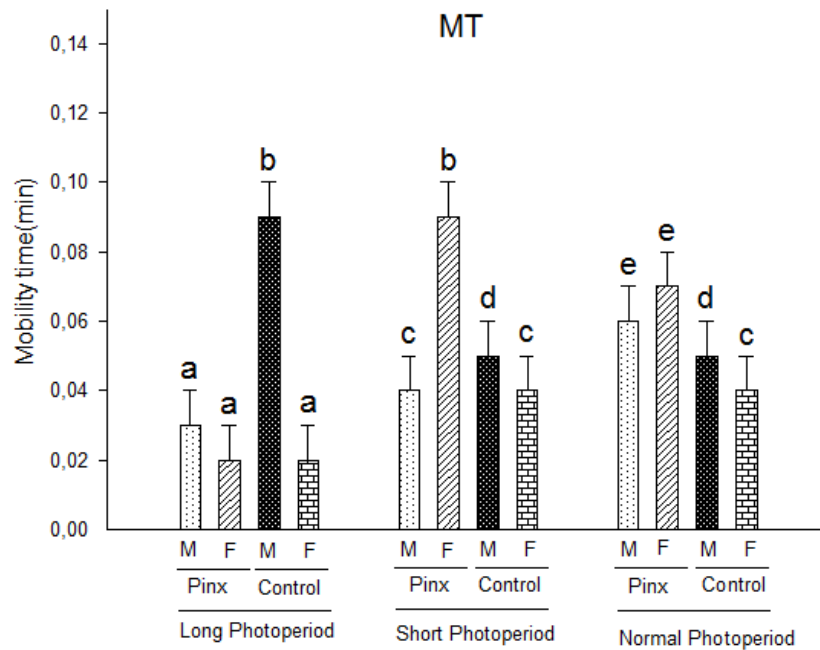


Figure 19.A Mean (S.E.M.) Mobility duration in porsolt. Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.2.3.2. Mobility Frequency (MF)

The main effect of the photoperiod was significant on the frequency of mobility in porsolt, $F(2,156) = 4.90$, $p = 0.009$. This means that juveniles ($M = 36.13$) born from mothers who were subjected to long photoperiod were more depressive than the others ($M_{\text{short}} = 60.45$ and $M_{\text{normal}} = 59.96$) born from mothers who were subject to short and normal photoperiods. There was a significant effect of interaction between photoperiod and pinealectomy $F(2,156) = 5.03$, $p = 0.008$. Birth from pinealectomized mothers decreases depression in short and normal photoperiod but increases depression in long

photoperiod. An interaction effect between the sex and photoperiod was significant, $F(2,156) = 4.47$, $p = 0.01$. Mobility frequency of female juveniles ($M = 69.81$) who borned from mothers were subjected to short photoperiod more than males ($M = 51.13$) who borned from mothers were subjected to short period but this situation that mobility frequency of male juvenile ($M = 52.89$) were more than female juvenile ($M = 19.38$) was opposite in long photoperiod. Mobility frequency were same each other with female juveniles ($M = 58.79$) borned from mothers were subjected to normal photoperiod and male juveniles ($M = 61.13$) borned from mothers were subjected to normal photoperiod. Moreover, there was significant effect of interaction between sex and pinealectomy, $F(1,156) = 8.62$, $p = 0.004$. Male juveniles ($M = 48.29$) borned from pinealectomized mothers were more depressive than female juvenile ($M = 64.02$) were borned from pinealectomized but this trend was opposite in control groups.

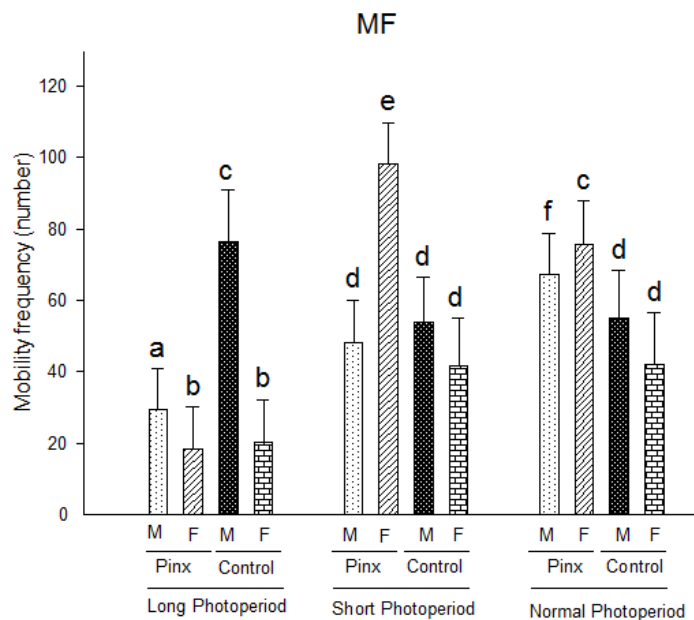


Figure 19.B Mean (S.E.M.) the frequency of mobility in porsolt. The figure explanations are represented in figure 19.A. a, b, c, d, e, f mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.2.3.4. Velocity (VEL)

The main effect of the photoperiod was significant in terms of the velocity of porsolt $F(2,156) = 11.75$, $p = 0.0001$. Velocity of juveniles who borned from mothers was subjected to long photoperiod decrease and juveniles borned from mothers were subjected to normal and short photoperiods were same velocity. There was a significant effect of sex $F(1,156) = 5.41$, $p = 0.02$. Male juveniles ($M = 369.12$) were faster than female juveniles ($M = 346.22$). An interaction effect between the photoperiod and pinealectomy was significant, $F(2,156) = 7.73$, $p = 0.001$, velocity of juveniles borned from pinealectomized mothers decrease in long photoperiod but in short and normal photoperiod increase velocity. There was significant effect of interaction between sex and photoperiod $F(2,156) = 10.57$, $p = 0.0001$. Moreover, an interaction effect between the sex and pinealectomy was also significant $F(1,156) = 8.64$, $p = 0.004$. Whereas, there was no significant differences velocity of pinealectomized males and females, in control group males ($M = 377.28$) were faster than females ($M = 325.44$).

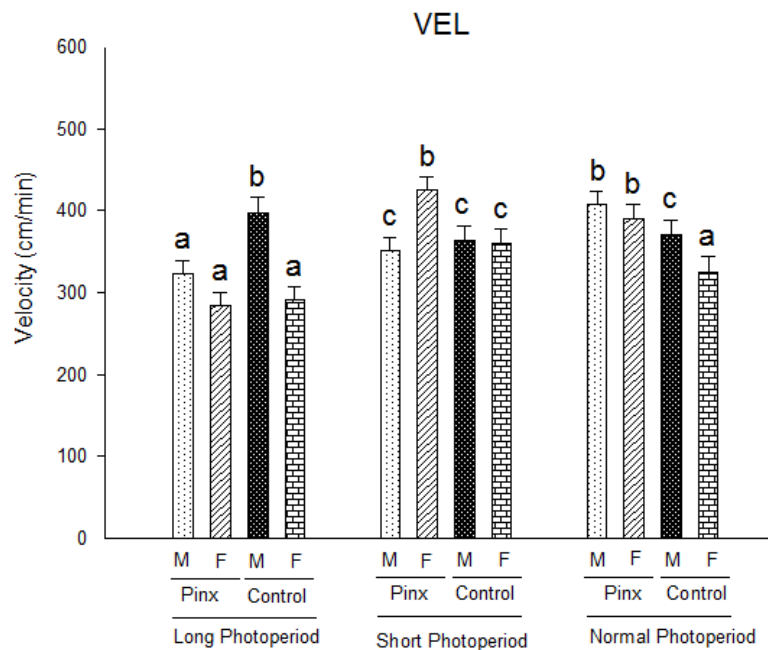


Figure 19.C Mean (S.E.M.) the velocity of the subjects in the porsolt. The figure explanations are represented in figure 19.A. a, b, c mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.3.5. The Summary of Porsolt result

According to parameter of mobility frequency, juveniles borned from mothers who were exposed to long photoperiod were more depressive than other all groups. Juveniles borned from pinealectomized mothers who were exposed to long photoperiod were more depressive than other juveniles according to mobility duration. Female juveniles borned from mothers who were exposed long photoperiod were more depressive but pinealectomy eliminate depression-like behaviours in female juveniles.

4.2.4. T -Maze Measurements

4.2.4.1. Total distance travelled on the t-maze (TDT)

An interaction effect between the photoperiod and sex was significant, $F(2,150) = 5.77$, $p = 0.004$. Female juveniles ($M_{\text{long}} = 196.98$ and $M_{\text{normal}} = 208.34$) born from mothers were subjected to long and normal photoperiods travelled more distance than male juveniles were born from mothers were subjected to ($M_{\text{long}} = 177.01$ and $M_{\text{normal}} = 149.43$) but this situation was opposite in short photoperiod. Travelled distance increased in all photoperiod, the increases were 77 units in short photoperiod, 58 units in long photoperiod and 44 units in normal photoperiod. Travelled distances increased in both juveniles were born from pinelectomized mothers (28 units) and juveniles were born from control mothers (92 units).

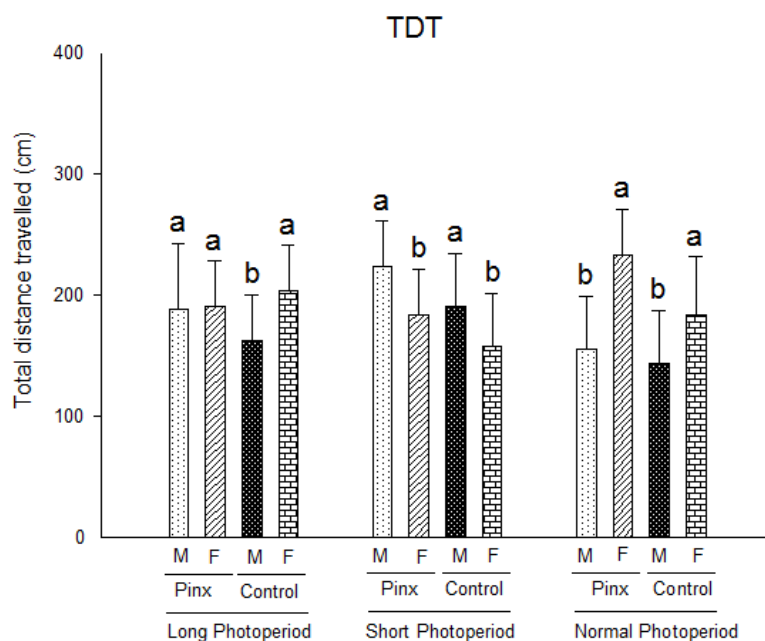


Figure 20.A Mean (S.E.M.) total amount distance travelled (TDT). Dotted striated bar represents pinealectomized male hamsters (n:8); right striated bar represents pinealectomized female hamsters (n:8); dark striated bar represents control male hamsters (n:8); bricks striated bar represents control female hamsters (n: 8); M: male; F: female; pinx: pinealectomy. a, b mean-values with the same letters within vertical columns are not significantly different ($p > 0.05$).

4.2.4.2. Total time spent for finding award (TSFA)

An interaction effect between the photoperiod and sex was significant, $F(2,150) = 6.60$, $p = 0.002$. Although, female juveniles ($M = 0.061$) borned from mothers were subjected to normal photoperiod spent more time than males juveniles ($M = 0.049$) for finding award, male juveniles ($M = 0.047$) borned to from mothers were subjected to short photoperiod spent more time than female juveniles ($M = 0.035$) in the same photoperiod for finding award and there was no differences spent time for finding award

between male juveniles ($M=0.054$) and female juveniles ($M=0.044$) in long photoperiod.

Whereas mothers were treatment with pinealectomy decrease total time spent for finding award in juveniles, total time spent for finding award increased in control groups.

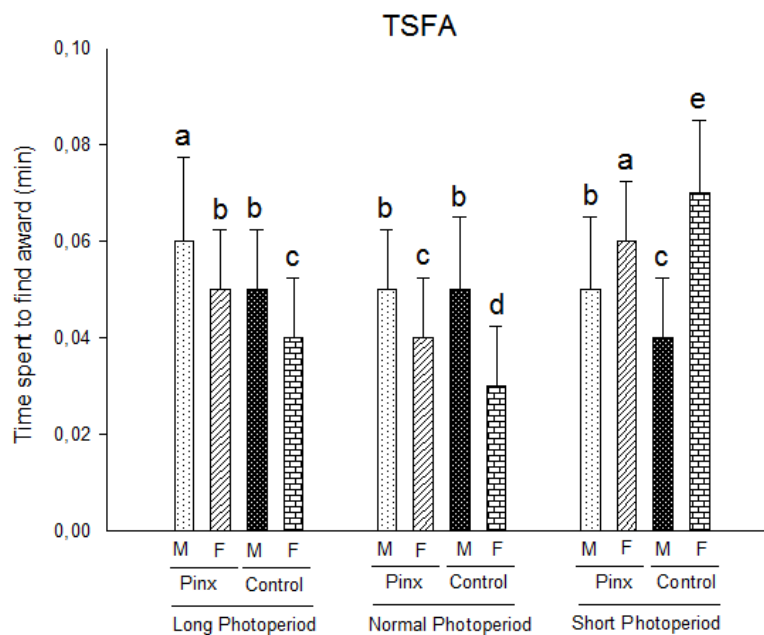


Figure 20.B Mean (S.E.M.) the total time spent for finding award (TSFA). The figure explanations are represented in Figure 20.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.4.4. Time Spent At The Decision Zone Of The T-Maze

An interaction effect between the photoperiod and sex was significant, $F(2,150) = 8.02$, $p=0.0001$. Whereas male juveniles ($M=0.028$) borned from mothers were subjected to long photoperiod spent more time spent at the decision zone of t-maze than female juvenile ($M=0.021$) in same photoperiod, female juvenile ($M=0.018$) borned from mothers were subjected to normal photoperiod spent more time spent at

the decision zone of T-maze than male juveniles ($M=0.013$) in same photoperiod and there was no differences on the total time spent at the decision zone of t-maze between female juveniles ($M=0.029$) borned from mothers subjected to short photoperiod and males ($M=0.026$) were born from mothers subjected to short photoperiod. The total time spent at the decision zone decreased in male juveniles and there was no differences total time spent at the decision zone in female juveniles.

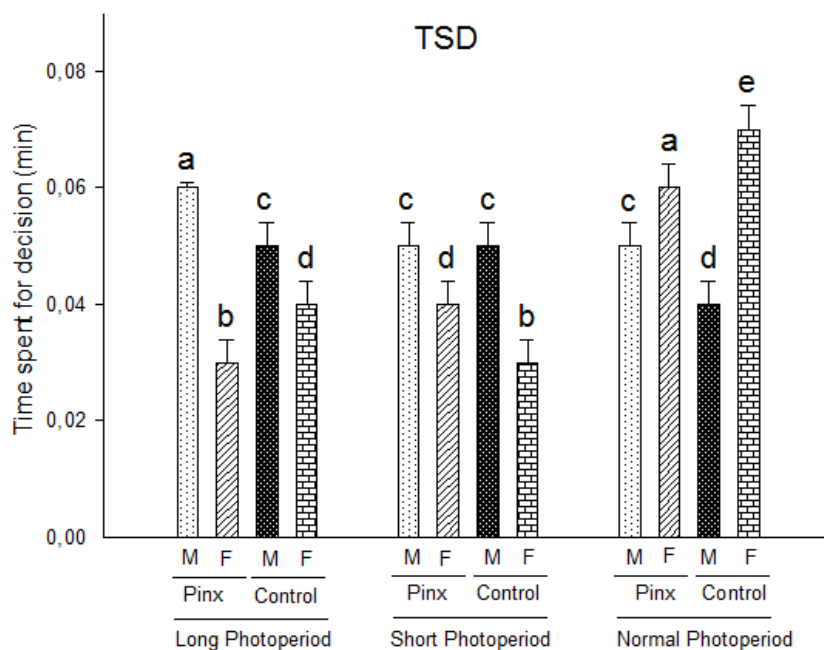


Figure 20.C Mean (S.E.M.) the total time spent at the decision zone of T-maze (TSD). The figure explanations are represented in Figure 20.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.4.5. Velocity (VEL)

The main effect of the photoperiod was significant on velocity in T- maze $F(2,150) = 4.04$, $p=0.02$. Long and short photoperiod increased velocity of juveniles. There was significant effect of measurement, $F(3,148) = 3.11$, $p=0.03$. There was also significant effect of sex $F(1,150) = 12.71$, $p=0.0001$. Female juveniles ($M = 748.74$)

were faster than male juveniles ($M=670.90$). An interaction effect between the photoperiod and sex was significant, $F(2,150)=12.15$, $p=0.0001$. Female juveniles ($M_{\text{long}}=781.70$ and $M_{\text{short}}=831.99$) borned from mothers were subjected to long and short photoperiod were faster than male juveniles ($M_{\text{long}}=646.68$ and $M_{\text{short}}=659.04$) borned from mothers were subjected to long and short photoperiod but this trend was opposite in normal photoperiod. Although pinealectomy increased velocity of subjects, velocity was low in control groups.

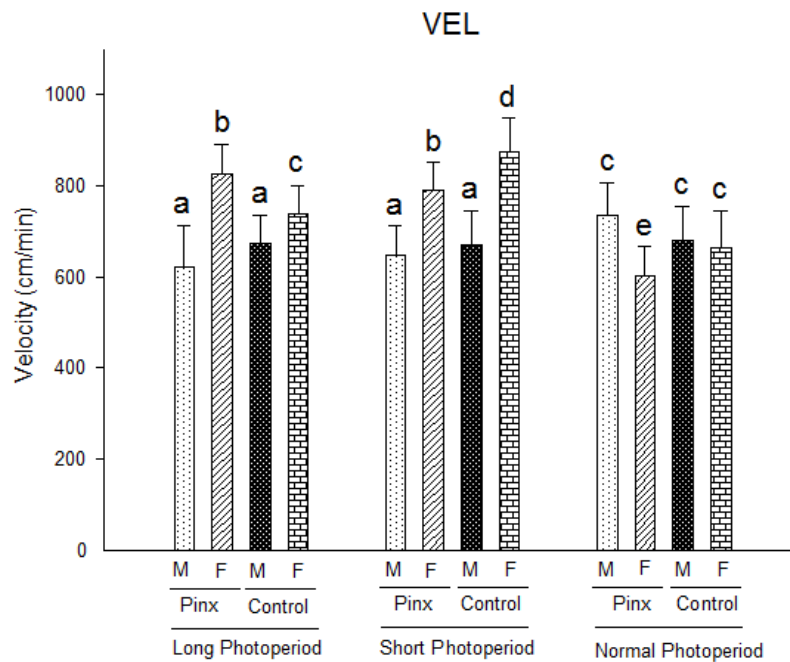


Figure 20.D Mean (S.E.M.) the velocity of subjects in the T-maze. The figure explanations are represented in Figure 20.A. a, b, c, d, e mean-values with the same letters within vertical columns are not significantly different ($p>0.05$).

4.2.4.6. The Summary of T-Maze Results

There were no direct effect of photoperiod, pinealectomy, and sex on the total time spent for finding award. Both male juveniles borned from mothers were exposed to normal photoperiod female juveniles borned from mothers who were exposed short photoperiod spent less time for finding award but there was no differences between male juveniles and female juveniles borned from mothers were exposed to long photoperiod. Female juveniles had high velocity.

4.3. RESULTS OF THIRD STUDY

4.3.1. Open Field Measurements

4.3.1.1. Total distance travelled on the open field (TDT)

The main effect of the measurement time was significant on the total distance travelled in the open field, $F(3,116) = 2.76$ $p = 0.05$. Groups ($M = 1734.95$) were more travelled at 12:00 than groups ($M = 1407.96$) at 24:00. There was significant effect of interaction between measurement time and treatment $F(6,116) = 2.54$, $p = 0.02$.

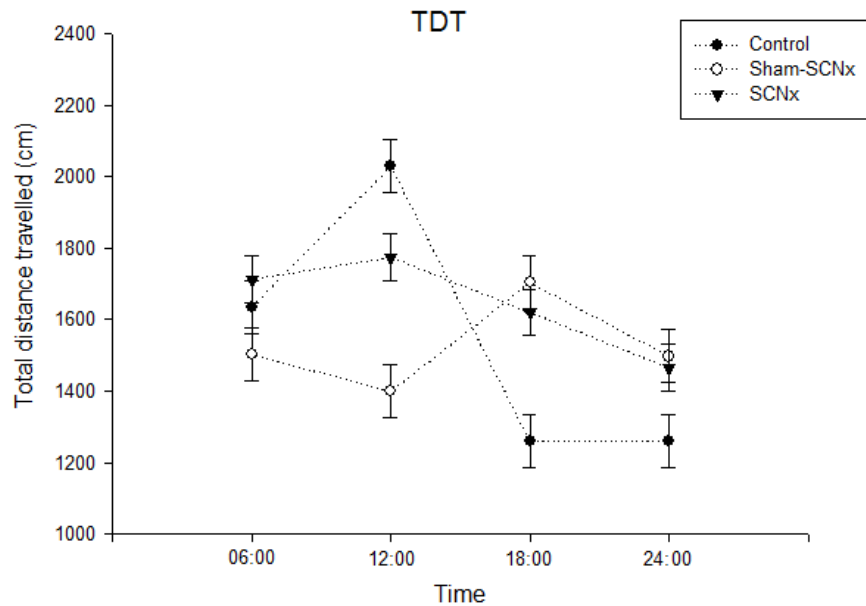


Figure 21.A Mean (S.E.M.) total amount distance travelled (TDT). Dark circular represents control rats (n:20); open circular represents Sham-SCNx rats (n:20); triangle represents lesion of SCN (SCNx) (n:20).

4.3.1.2. Time spent at the center of the open field (TSCO)

The main effect of the measurement time was significant in amount of time spent in the center of the the open field, $F(3,116) = 2.58$ $p = 0.05$. There were significant differences between time 12:00 hr ($M = 0.55$) between the time 18:00 hr ($M = 0.09$). Group of time 12:00 hr spent the most time in the center of the the open field. The effect of the treatment was also significant according to the amount of time spent in the center of the open field $F(2,116) = 4.86$, $p = 0.01$. There were significant differences between control and SCNx. SCNx were less anxious because SCNx groups spent ($M = 0.52$) tme more time than Sham-SCNx ($M = 0.20$) and control ($M = 0.09$).

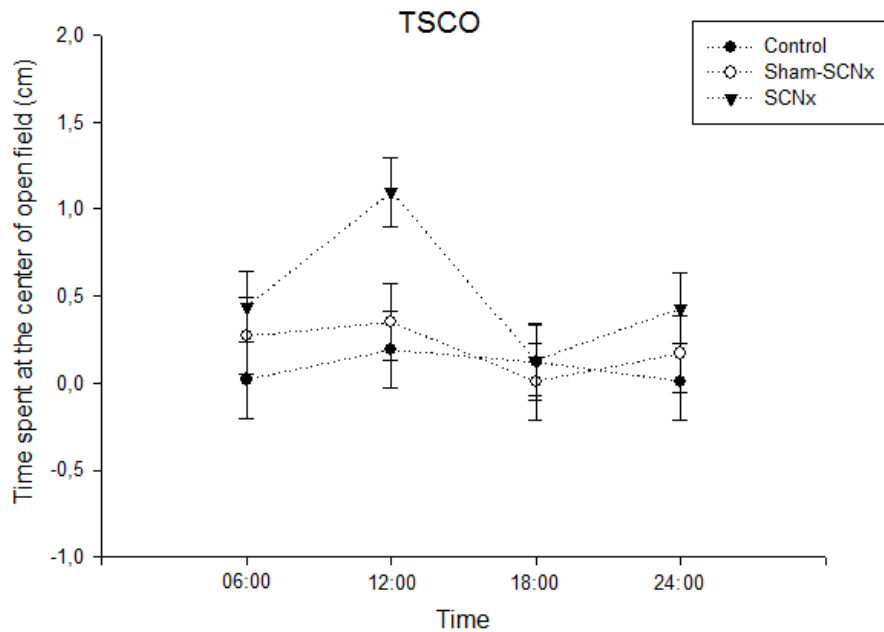


Figure 21.B Mean (S.E.M.) time spent at the center of the open field (TSCO). The figure explanations are represented in Figure 21.A.

4.3.1.2. The Frequency of zone transition in the open field (ZT)

The main effect of the treatment was significant on the frequency of zone transition in open field $F(2,116) = 3.31$, $p = 0.04$. There were significant differences between Sham-SCNx ($M = 1.85$) and SCNx ($M = 4.50$) according to on the frequency of zone transition.

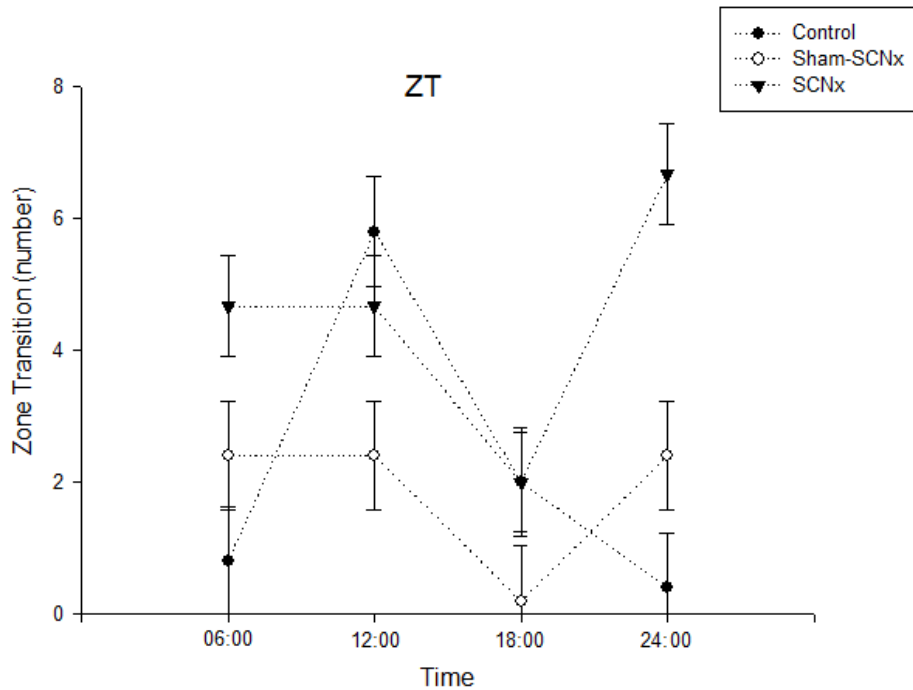


Figure 21.C Mean (S.E.M.) the frequency of zone transition in the open field (ZT). The figure explanations are represented in Figure 21.A.

4.3.1.3. Velocity (VEL)

The main effect of the measurement time was significant on the velocity in the open field, $F(3,116) = 2.81$, $p = 0.04$. There were significant differences between the time 12:00 hr ($M = 348.04$) and the time 24:00 hr ($M = 282.09$). Subjects of the time 24:00 hr were slower than time 12:00 hr. There was significant effect of interaction between measurement time and treatment $F(6,116) = 2.54$, $p = 0.02$. This means that, whereas, controls ($M = 407.20$) were more faster than SCNx ($M = 355.95$) and Sham-

SCNx ($M=280.96$) at 12:00 hr; controls ($M_{18:00\text{hr}}=252.75$ and $M_{24:00\text{hr}} = 252.74$) were less faster than SCNx ($M_{18:00\text{hr}}=324.66$ and $M_{24:00\text{hr}}=292.09$) and Sham-SCNx ($M_{18:00\text{hr}}=341.14$ and $M_{24:00\text{hr}}=300.44$) both at 18:00 hr and 24:00 hr.

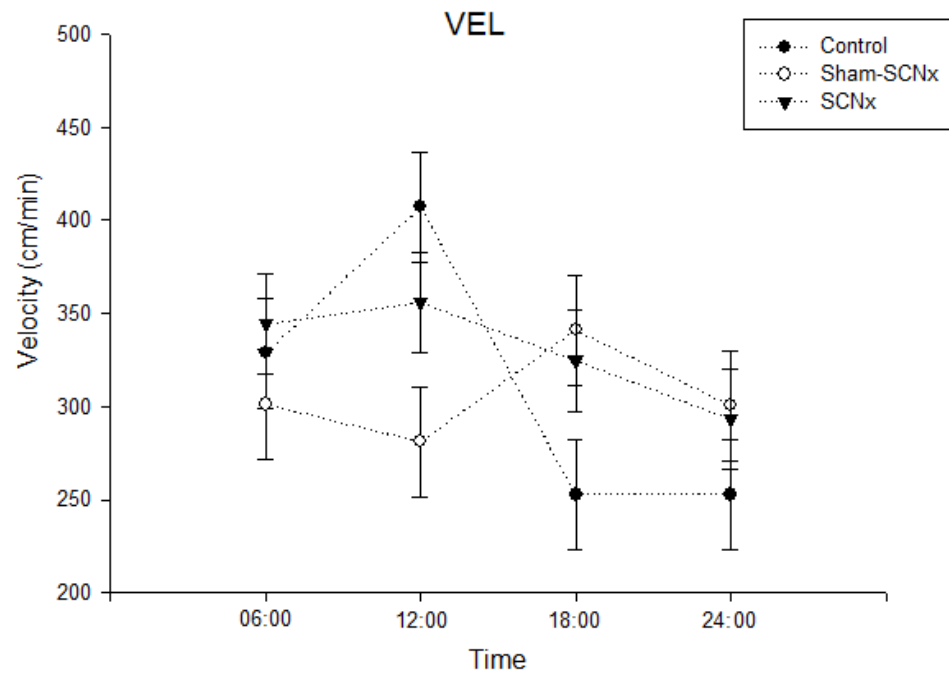


Figure 21.D Mean (S.E.M.) the velocity of the subjects in the open field (VEL). The figure explanations are represented in Figure 21.A.

4.3.1.4. The Summary of Open Field Results

Group of time 12:00 hr spent the most time in the center of the the open field so they had low anxiety level. Lesion groups were less anxious than control and sham-lesions groups.

4.3.2 Elevated Maze Measurements

4.3.2.1. Total distance travelled on the elevated arm maze (TDT)

The main effect of the treatment was significant on the total distance travelled, $F(2,116) = 3.67$, $p = 0.03$. There were significant differences between Sham-SCNx ($M = 870.20$) and SCNx ($M = 1044.10$), SCNx groups travelled more distance than Sham-SCNx. There was significant effect of interaction between measurement time and treatment $F(6,116) = 3.85$, $p = 0.002$.

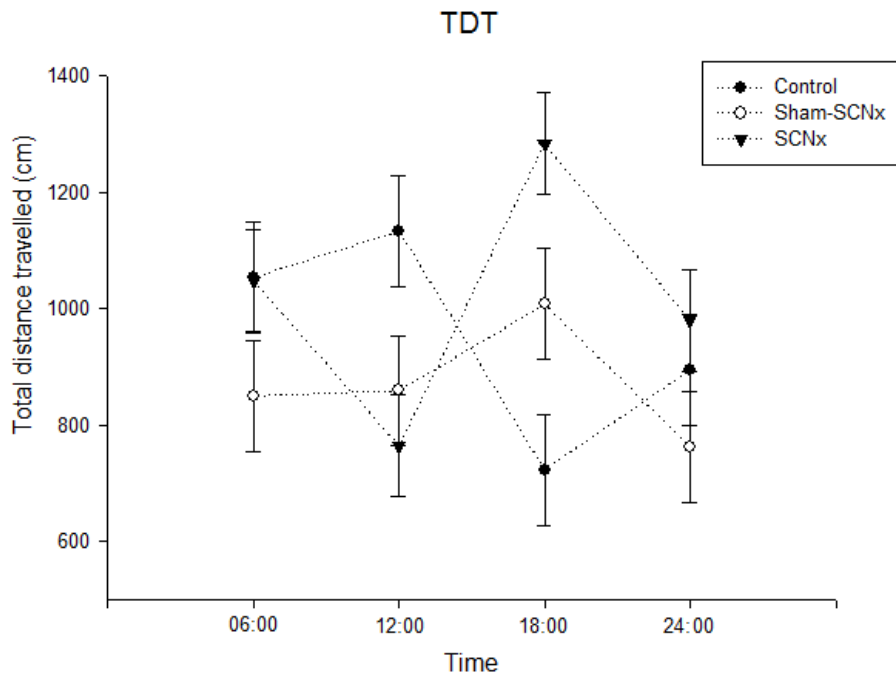


Figure 22.A Mean (S.E.M.) Total amount distance travelled (TDT). Dark circular represents control rats (n: 20); open circular represents Sham-SCNx rats (n: 20); triangle represents lesion of SCN (SCNx) (n:20).

4.3.2.2. Time spent in open arms (TSOA)

The effect of the measurement time was significant on the time spent in open arms $F(3,116) = 4.09$, $p = 0.01$. Subjects spent more ($M = 2.03$) time than the others ($M_{06:00\text{hr}} = 1.58$ and $M_{24:00\text{hr}} = 1.14$ and $M_{12:00\text{hr}} = 1.16$) in open arms at 18:00 hr. In this group had low anxiety level. The main effect of the treatment was significant $F(2,116) = 18.31$, $p = 0.0001$. SCNx groups which were less anxious spent more time than control and Sham-SCNx. These results were parallel results of open field.

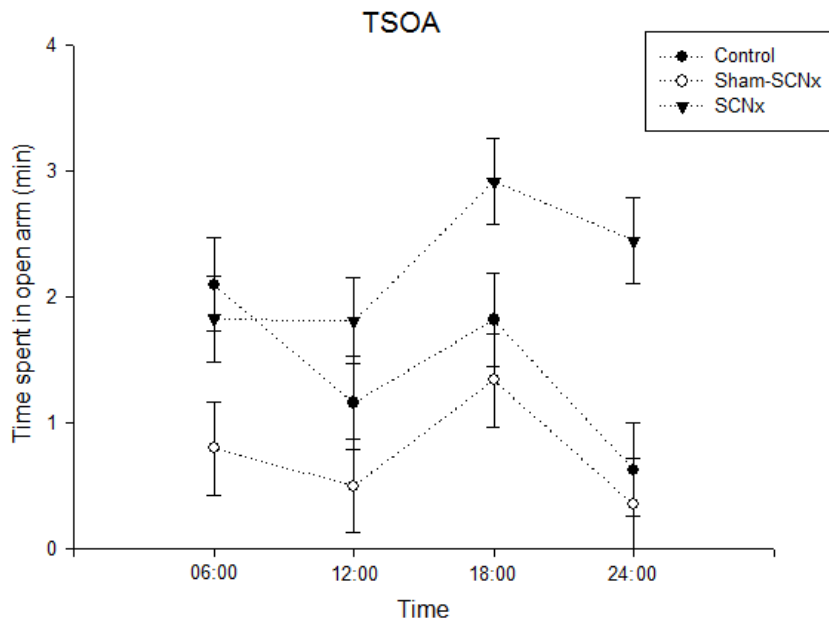


Figure 22.B Mean (S.E.M.) time spent in open arms. The figure explanations are represented in Figure 22.A.

4.3.2.3. Mobility in Elevated maze (MT)

The main effect of the treatment was significant on the mobility $F(2,116) = 2.84$, $p = 0.05$. SCNx ($M = 0.009$) were more mobile than controls ($M = 0.003$).

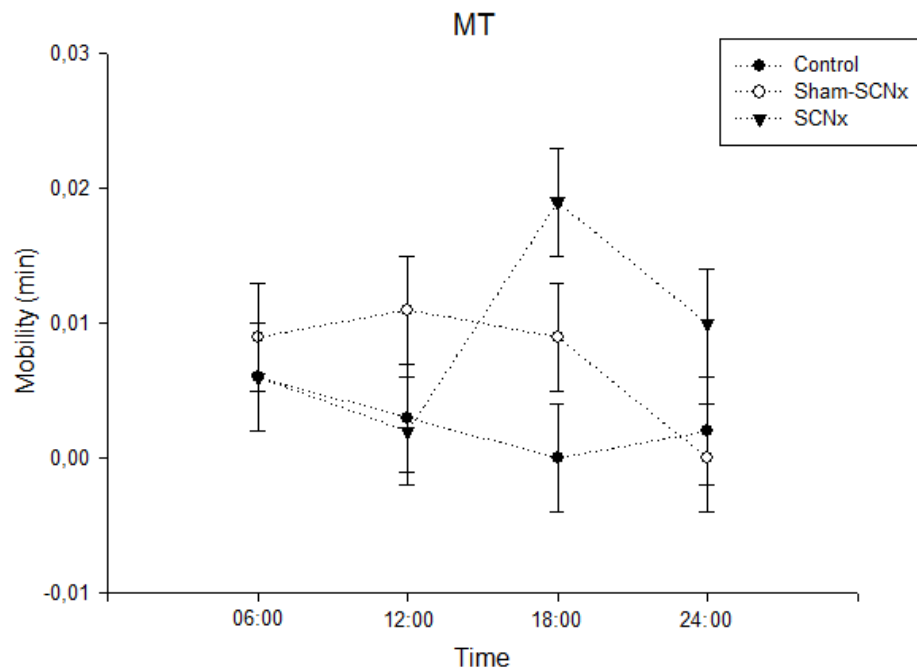


Figure 22.C Mean (S.E.M.) mobility time in elevated plus maze. The figure explanations are represented in Figure 22.A.

4.3.2.4. Velocity in elevated maze (VEL)

There was a significant effect of treatment on velocity, $F(2,116) = 3.69$, $p = 0.03$. There were significant differences between Sham-SCNx ($M = 174.41$) and SCNx ($M = 209.30$), SCNx groups were faster than Sham-SCNx. There was significant effect of interaction between measurement time and treatment $F(6,116) = 3.92$, $p = 0.001$.

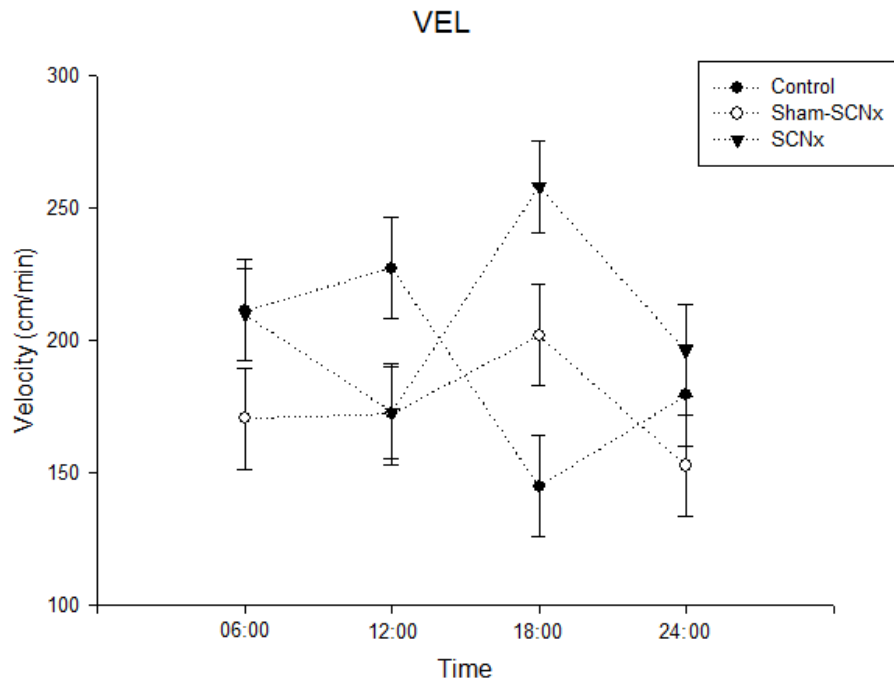


Figure 22.D Mean (S.E.M.) velocity in elevated plus maze. The figure explanations are represented in Figure 22.A.

4.3.2.5. The Summary of Elevated Plus Maze Results

Lesion groups were less anxious than sham-SCNx and intact groups according to on the time spent in open arms.

4.3.3. Forward Swim Test (Porsolt) Measurements

4.3.3.1. Total distance travelled on the porsolt (TDT)

The main effect of measurement time was significant on the total distance travelled on porsolt, $F(3,116) = 46.31$, $p = 0.0001$. Subjects ($M = 4082.48$) travelled more distances than others ($M_{06:00hr} = 1586.55$ and $M_{24:00hr} = 2282.29$ and $M_{12:00hr} = 1746.69$) at 18:00 hr.

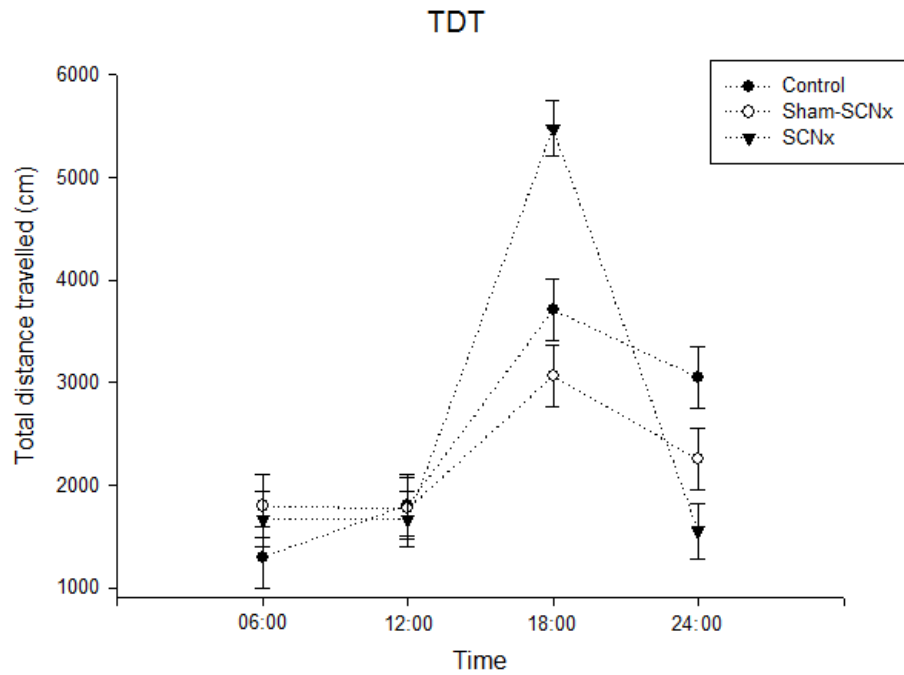


Figure 23.A Mean (S.E.M.) total amount distance travelled (TDT) in porsolt. Dark circular represents control rats (n: 20); open circular represents Sham-SCNx rats (n: 20); triangle represents lesion of SCN (SCNx) (n:20).

4.3.3.2. Mobility Duration (MT)

The effects of the measurement time significant in the terms of mobility duration in porsolt $F(3,116) = 4.80$, $p = 0.003$. Subjects ($M = 0.164$) spent more time than the others ($M_{06:00\text{hr}} = 0.246$ and $M_{24:00\text{hr}} = 0.164$ and $M_{12:00\text{hr}} = 0.239$) in mobile at 24:00 hr.

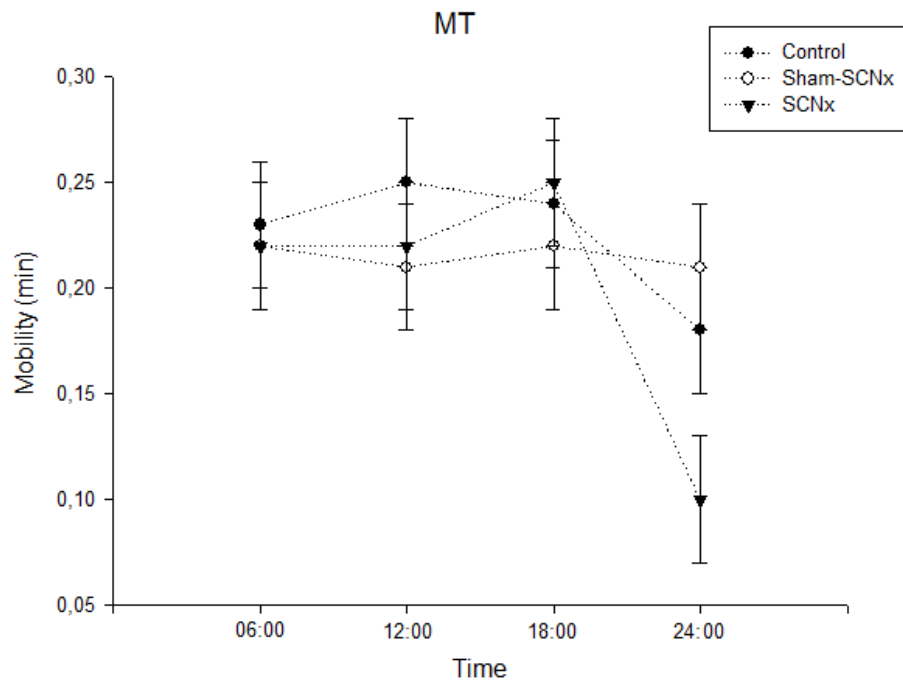


Figure 23.B Mean (S.E.M.) Mobility duration of subjects in porsolt. The figure explanations are represented in Figure 23.A.

4.3.3.3. Mobility Frequency (MF)

The main effect of the measurement time was significant on the frequency of mobility in porsolt $F(3,116) = 9.01$ $p = 0.0001$. There were significant differences between time 24:00 hr ($M = 125.20$) between the time 18:00 hr ($M = 202.96$).

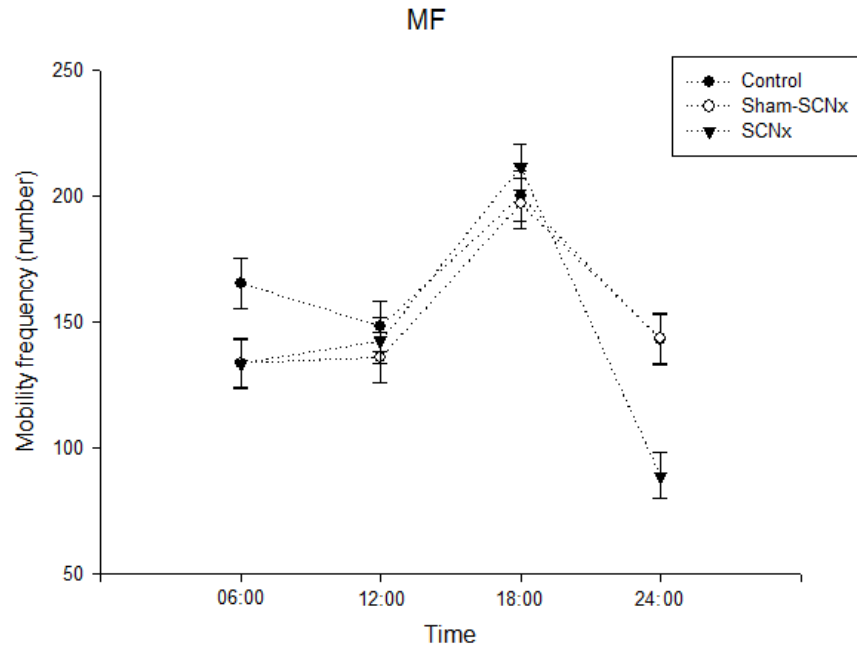


Figure 23.C Mean (S.E.M.) the frequency of mobility in porsolt. The figure explanations are represented in Figure 23.A.

4.3.3.4. Velocity in porsolt (VEL)

The main effect of the measurement time was significant on the velocity in porsolt $F(3,116) = 29.92$ $p = 0.0001$. The ordering of velocity were at 18:00 hr, at 24:00 hr and then 06:00, 12:00. There were no significant differences between time 06:00 hr ($M = 462.66$) between the time 12:00 hr ($M = 457.24$). There was significant effect of interaction between measurement time and treatment $F(6,116) = 8.88$ $p = 0.0001$. The SCNx groups ($M_{24:00hr} = 403.21$ and $M_{18:00hr} = 1272.44$) at 24:00 hr and 18:00 hr were more significance differences than Sham-SCNx ($M_{24:00hr} = 709.55$ and $M_{18:00hr} = 623.88$) and control ($M_{24:00hr} = 717.42$ and $M_{18:00hr} = 940.92$)

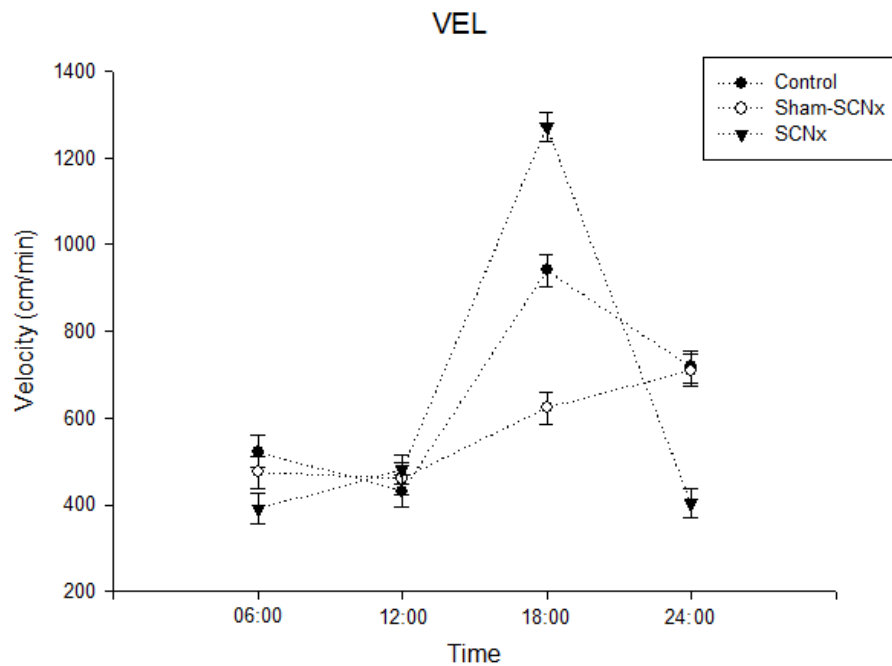


Figure 23.D Mean (S.E.M.) the velocity of the subjects in Porsolt. The figure explanations are represented in Figure 23.A.

4.3.3.5. The Summary of Porsolt Results

According to parameter of mobility duration, groups at 24:00 hr were more depressive. Groups at 18:00 hr were more travelled distance and they had high velocity so they were less depressive. There was no effect of lesion.

4.2.5 Water Maze Measurements

4.2.5.1. Total distance travelled on the Morris water maze

The main effect of the presence of treatment was significant on the total distance travelled on the Morris water maze, $F(2,116) = 3.35$, $p = 0.03$. SCNx ($M = 1973.39$) groups travelled more distance than Sham-SCNx ($M = 924.74$) and control ($M = 1094.72$).

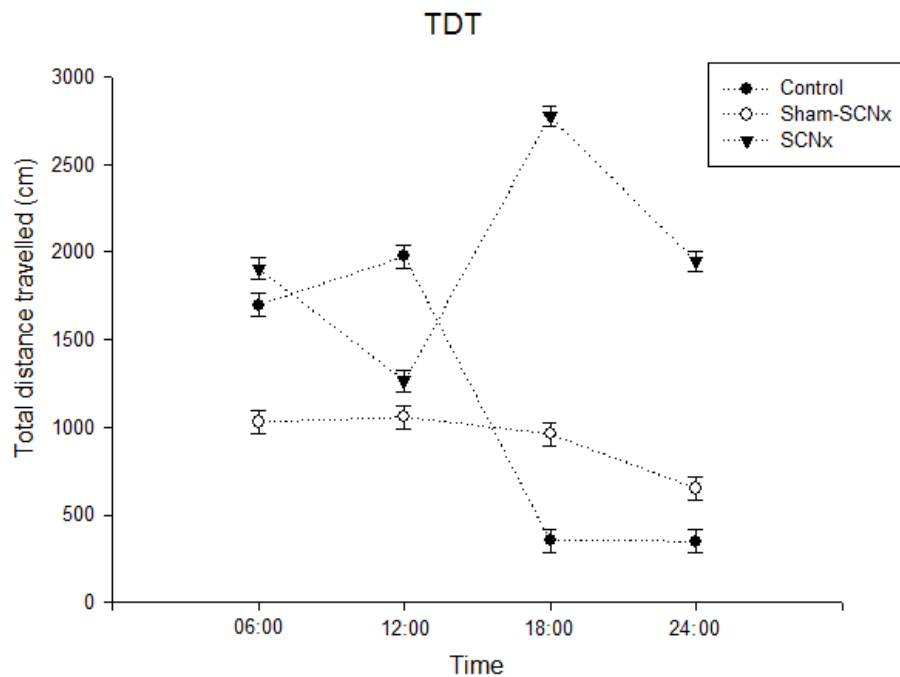


Figure 24.A Mean (S.E.M.) total amount distance travelled (TDT). Dark circular represents control rats (n: 20); open circular represents Sham-SCNx rats (n: 20); triangle represents lesion of SCN (SCNx) (n:20).

4.2.5.2. Time spent to find the platform (TSFP)

The main effect of the presence of the measurement time was significant on the time spent to find the platform on the Morris water maze, $F(3,116) = 4.44$, $p = 0.005$. There were significant differences between at 24:00 hr ($M = 0.33$) and 12:00 hr ($M = 0.89$). There were also significant differences between at 24:00 hr ($M = 0.33$) and 06:00 hr ($M = 0.77$). Subjects spent more time at 12:00 hr. There was significant effect of interaction between measurement time and treatment $F(6,116) = 2.86$, $p = 0.01$.

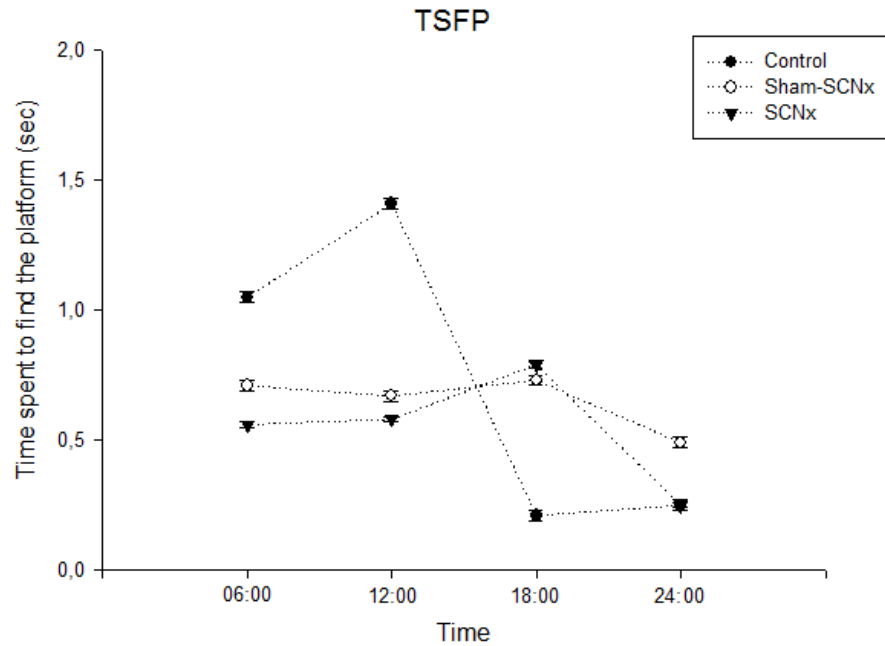


Figure 24.B Time spent to find the platform. The figure explanations are represented in Figure 24.A.

4.2.5.3. Time spent in the quadrant of the platform (TSCQ)

The main effect of the presence of the measurement time was significant on the time spent in the quadrant of the platform on the Morris water maze, $F(3,116) = 4.85$, $p = 0.003$. Subjects ($M = 0.19$) spent more time than the others ($M_{06:00hr} = 0.17$ and $M_{24:00hr} = 0.08$ and $M_{18:00hr} = 0.12$) at 12:00 in the quadrant of the platform. There was significant effect of interaction between measurement time and treatment $F(6,116) = 3.35$, $p = 0.004$.

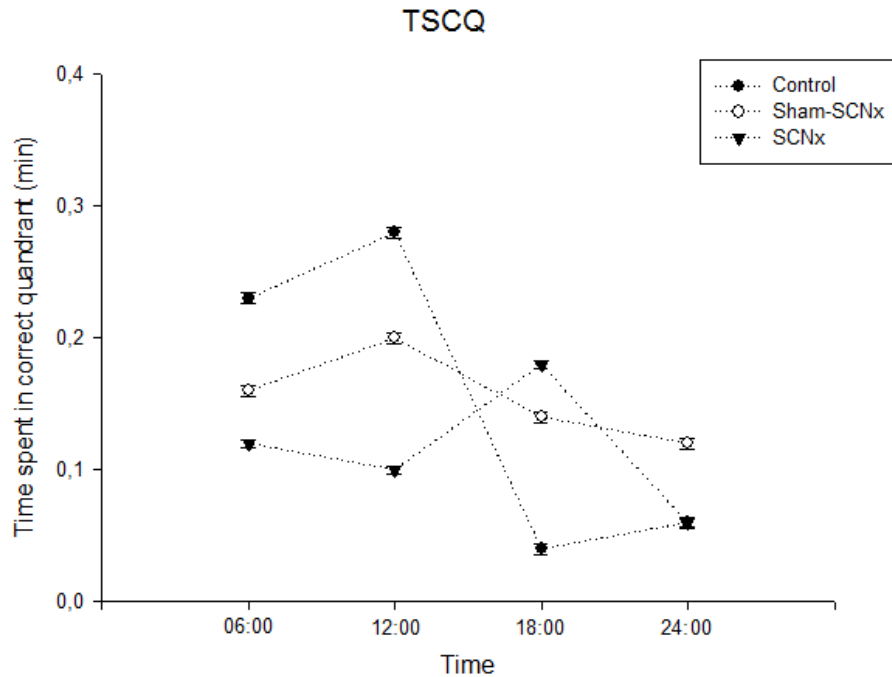


Figure 24.C Time spent in the quadrant of the platform in the Morris water maze is represented. The figure explanations are represented in Figure 24.A.

4.2.5.4. Velocity in Morris water maze (VEL)

The main effect of the presence of the measurement time was significant on the velocity in Morris water maze $F(3,116) = 5.07$ $p = 0.002$. Subjects ($M = 3907.47$) were the most faster than others ($M_{06:00hr} = 1884.47$ and $M_{12:00hr} = 1693.57$ and $M_{18:00hr} = 2028.95$) at 24:00 hr. There was no significant among other times. The effect of the presence of treatment was significant on the velocity in Morris water maze $F(2,116) = 11.19$ $p = 0.0001$. Whereas SCNx ($M = 3860.38$), were the most faster, there was no differences between Sham-SCNx ($M = 1673.75$) and control ($M = 1601.72$). There was significant effect of interaction between measurement time and treatment $F(6,116) = 6.53$ $p = 0.0001$. There were significant differences among groups in all times.

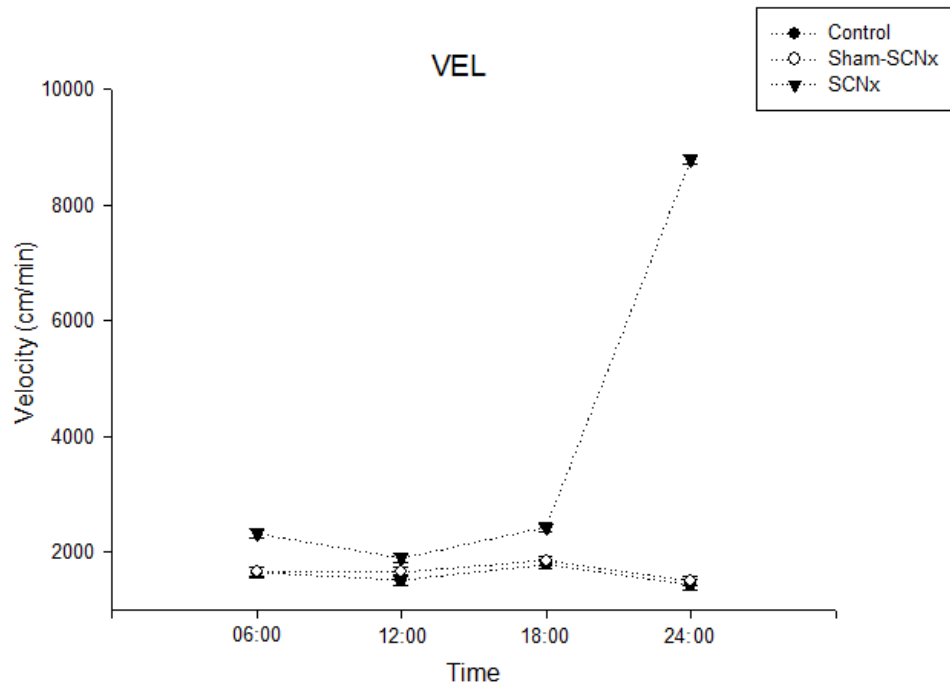


Figure 24.D Mean (S.E.M.) the velocity of the subjects in the Morris water maze is represented. The figure explanations are represented in Figure 24.A.

4.2.5.4. The Summary of Morris Water Maze Results

According to parameter of time spent for finding award, subject's spatial memory was lowest at 12:00 hr. Parameter of velocity supports this parameter. Whereas lesion groups were more travelled distance than others and they had high velocity, there was no significant difference between lesion and other groups in terms of time spent for finding award.

5. DISCUSSION

The results of the present study can be classified under three main headings: anxiety-like behaviour (in open field apparatus and elevated plus maze), depression (forced swim test) and spatial memory performance (in T-maze).

5.1. Discussion of the First Study

5.1.1. Anxiety-Like Behaviours

Motor functions such as spontaneous activity is measured by the open field. Open field test is also used to measure the anxiety like behavior in rodents (Benabid et al., 2008). The total distance traveled, the total number of entries to the center and the edge of the open field, the time spent in the center of the open field versus time spent at the edge of the open field and the mobility are frequently used parameters measured in open field test in the literature (Pyter and Nelson, 2006). In this maze, if the anxiety of the animal is high, the number of the entries to the edge of the open field is increasing and the total distance traveled is decreasing. The total number of the entries into the center and the edges provides a built-in control measure for general hyperactivity or sedation.

The elevated plus maze has been one of popular or widely used test to measure the anxiety like behaviours (Dawson and Tricklebank, 1995). In this maze, if the anxiety of the animal is high, the number of the entries to closed arms is increasing and the total distance traveled is decreasing. The total number of the entries into all arms provides a built-in control measure for general hyperactivity or sedation.

In open field and elevated maze tests pinealectomy reduced the anxiety especially in females. It is well known fact that pinealectomy abolishes the rhythmic endogenous melatonin release and decreases the plasma levels of melatonin significantly (Hardeland et al., 2006). However, the present finding indicating the low level of anxiety due to pinealectomy in hamsters is inconsistent with the previous research finding (Kaya et al., 2011) that indicated no significant effect of pinealectomy on anxiety in rats. The previous studies have suggested that pinealectomy alone did not have a significant effect on anxiety behavior (Kovács et al., 1974; Juszczak et al., 1996) (Quay, 1970; Finkelstein, 1978). Thus an interaction effect between pinealectomy and photoperiod in this experiment provided evidence for these studies mentioned earlier. This interaction clearly showed that a lack of melatonin hormone via pinealectomy and long photoperiod decreased anxiety-like behaviors. Such finding provides a supporting evidence for the previous studies mentioned above that suggested no significant role of pinealectomy alone. It also emerged a new research finding that pinealectomy interacted with photoperiod on the anxiety like behaviors.

Another plausible explanation for the difference between present finding and the previous studies is that hamsters may be more prone to effects of pinealectomy than rats. Such difference makes a sense since the release of the melatonin hormone in rats shows a diurnal pattern which shows a gradual rise and one peak level during night (Illnerova et al., 1983; Reiter, 1993), whereas that in hamsters shows a diurnal pattern but shows a relatively short interval and two peak levels during night (Reiter, 1993). Melatonin levels in hamsters also reaches peak levels earlier than those in rats during long photoperiod (Stetson and Tay, 1983; Reiter, 1993). This also provides evidence for why hamsters are photoperiodic animals. Such slight differences suggest that a decrease in melatonin level via the removal of pineal gland may produce profound

effect in hamsters along with long photoperiod. Consistent with this explanation, our result did provide evidence of a significant effect of pinealectomy on anxiety like behaviors in Syrian hamsters. Obviously a comparative future research in a single research paradigm that compares hamsters with rats is needed for shedding lights on how these differences produces patterns on anxiety like behaviors.

The present research, moreover, provided evidence that females are more likely to be affected by pinealectomy than males. In other words, males were more anxious than females in open field and elevated plus maze. There may be some plausible explanations for this sex difference. One plausible explanation for a stronger effect of photoperiod in females over males is the selectivity hypothesis developed by Meyers-Levy (1989). This proposes that females tend to process information comprehensively, processing all available information both relevant and irrelevant. Such information processing in females may contribute to a low level of anxiety besides the low amount of melatonin and disorganization of circadian rhythm. In contrast, males tend to process information in a more selective fashion, focusing only on what is relevant to the task or to themselves. Such conservative system may lead males to focus on specific information. However, there is no specific information for males in the open field. Such an environment may increase the anxiety levels of males. The present experiment showed that pinealectomy lowered anxiety of males in open field. In the elevated plus maze males travelled less distance than females. This indicated that males were more anxious than females. Since females tend to process the entire information, they have to travel more distance than males. Such activity might lower anxiety level of females.

Males spent more time than females in the open arm of elevated plus maze. This may show that males are still searching for important or specific information in such

environment. On the other hand, since females process more information or have it more quickly than males, they tend to stay in or search for a very safe place or closed arm instead of searching for the entire environment. Such searching behavior in closed arm may make females more anxious than males. Consistent with this, our finding showed that females were more anxious than males in this measure. Such effect was so strong that either low or high amount of melatonin level produced by short or long photoperiod enhanced the level of anxiety. This suggests that there may be curvilinear relationship between melatonin level and anxiety in females regarding time spent in closed arm.

Long photoperiod and pinealectomy both decreased melatonin level in organism. Such conditions were especially beneficial for lowering the anxiety level of males in open field and elevated plus maze. Pinealectomy also produce beneficial effect for lowering anxiety of females. Such veridical finding may suggest that pinealectomy lowered anxiety of hamsters regardless of sex differences. Such consistent finding is of crucial importance in the literature since no previous study has examined this so far. Long photoperiod also decreases the amount of melatonin in plasma since the light, which is first perceived by the retina of the eye, is transferred to the SCN as well as pineal gland through the retinohypothalamic tract. Such transference not only suppresses the releases of melatonin hormone in pineal gland but also disrupts the generation and the regulation of the circadian rhythms controlled by SCN. Both low amount of melatonin and dysfunction or disorganization of circadian rhythm may be responsible for the low amount of anxiety in hamsters. Our results also showed that photoperiod and pinealectomy treatment can be used interchangeably since the variances explained by these factors were almost the same across the different parameters of both open and elevated plus maze tests.

5.1.2. Depression-Like Symptoms

We evaluated the depressive- like responses (learned helplessness) of the subjects in forced swim test (Porsolt et al., 1977) consisted of an opaque cylinder tank which was filled with water. We examined the total distance travelled, mobile duration and mobile frequency. Depressive-like symptoms are low when the mobile duration is high.

The findings from the Porsolt showed that the subjects in the long photoperiod were less depressive than those in normal photoperiod and short photoperiod. This means that a low level of internal circulating melatonin may help animals cope with their depression. We also found that pinealectomy decreased the depression in males in line with our previous findings in anxiety and spatial learning in this study. However, these findings were not consistent with the previous studies indicating that exogenous administration of melatonin was a preventive factor for depression (Beck-Friis et al., 1985; Detanico et al., 2009; Mantovani et al., 2003; Micale et al., 2006; Prakhie and Oxenkrug, 1998; Shaji and Kulkarni, 1998). This difference may be due to the fact that endogenous melatonin has rather different consequences for an animal than exogenous melatonin. The time of administration of exogenous melatonin is of great importance here. When internal melatonin is high, exogenous melatonin administration may not be effective. On the other hand, when it is low, especially during the day light, exogenous melatonin administration may have beneficial effect for increasing the level of melatonin in animal body. The evidence for this possibility comes from a recent study that demonstrating that the measurement time plays an important role in obtaining either beneficial or detrimental effect of melatonin in anxiety like behaviors (Kaya et al., 2011).

In addition we found that males were more immobile than females in the normal and short photoperiod but they were the same in the long photoperiod. This means that males were more depressive than females in the normal and short photoperiod but not the long photoperiod. This finding is consistent with the findings of the previous study (Dala et al., 2008) showing that when exposed to uncontrollable stress, male rats tend to show more learned helplessness than females do. In line with this finding, we also found that pinealectomy decreased depression in males but did not affect it in females in terms of mobility and mobility frequency. We suggest that hormonal changes may play important role here since females in contrast to males are more prone to hormonal changes such as estrus depending on the time period. Why females are not affected by pinealectomy needs a detailed investigation in the future.

5.1.3. Spatial Memory Performance

The present study has shown that in T-maze test, in a similar fashion, long photoperiod and pinealectomy enhanced the spatial memory in females. This outcome can be attributed to the low levels of melatonin. Since the pineal gland is surgically removed, the rhythmic endogenous melatonin release is abolished (Hoffman and Reiter, 1965). In the previous studies we have also found that exogenous melatonin administration produced detrimental effect on spatial learning (Karakas et al., 2011; Coskun et al., 2012). In the present study, it was also determined that the pinealectomized subjects were faster than normal subjects in the long photoperiod. This suggests that both pinealectomy and long photoperiod lead to a low level of melatonin, which, in turn, facilitates spatial learning. One might consider that which one of these factors is more effective than other. We determined that an interaction effect of these factors (partial eta square is around .10 for this interaction) is more

determining factor on such behavior than the only pinealectomy or long photoperiod (partial eta square is around .06 for either pinealectomy or long photoperiod). However, the findings of the present study were not consistent with the previous study (Karakas et al., 2011) that indicated the pinealectomy decreased the spatial memory capacity on the Morris Water maze. This difference can be attributed to the testing technique used in the previous and the present study. In the present study we used T maze, whereas we used the Morris water maze in our previous study. The Morris Water maze requires more energy expenditure than T maze since it requires that an animal must swim while searching for the platform (Jardim et al., 1999). In short, an animal needs to pay attention to the two sources; one for finding platform and one for swimming. Thus a low level of melatonin due to the pinealectomy harms spatial memory performance in the Morris water maze more than T maze that requires relatively the low level of energy.

The present study showed that males learnt slower than females. This finding is also consistent with the recent research finding which indicates that female rats learnt better than male rats in the recognition task (Sutcliffe et al., 2007). In addition, the research finding in human studies demonstrated that females displayed better recognition performance than males (Mc Givern et al., 1997). Underlying the photoperiodic reduction of brain mass and function in this species are reductions in the mass of reproductive tissues and testosterone (current study; Pyter et al., 2005a,b, 2006; Workman et al., 2009). Testosterone impairs CA1 LTP in rats (Harley et al., 2000) and alters hippocampal synaptic plasticity in *Mus* (Sakata et al., 2000). Although species differences among rodents in the effects of testosterone on hippocampal function and LTP remain unspecified, the present study argues against testosterone impairing hippocampal LTP in white-footed mice, as the SD mice (low testosterone) reduced

LTP. SD deficits in spatial learning and memory can be rescued with testosterone; however, removal of testosterone from LD mice did not impair spatial learning and memory, and neither testosterone nor photoperiod altered androgen receptor expression in the hippocampus (Pyter et al., 2006).

The difference between males and females in learning performance can be attributed to the selectivity difference between males and females in searching for the relevant cues in the available environment. The selectivity hypothesis developed by Meyers-Levy (1989) proposes that females tend to process information comprehensively, processing all available information both relevant and irrelevant. Such information processing in females may contribute to a high level of learning. In contrast, males tend to process information in a more selective fashion, focusing only on what is relevant to the task or to them. Such information processing may lead males to focus on specific information, ignoring the other relevant cues in the environment. We also found that males learnt faster than females in the long photoperiod; however, males learnt slower than females in both short and normal photoperiod. This means that a low level of melatonin due to long photoperiod enhanced spatial learning performance of males. In other words, from the perspective of selectivity hypothesis, a low level of melatonin may help males focus on the information comprehensively.

Also, hormonal differences between males and females can contribute to the learning differences between males and females. Estrogen hormone can play an important role in regulating spatial memory. The initial studies using the spatial radial arm maze have suggested that estradiol exerts differential dose-dependent effects on spatial working memory processes (Frye, 1995; Holmes et al., 2002; Luine et al., 1998; Warren and Juraska, 1997). The low levels of estradiol reduce working memory errors, whereas high levels of estradiol increase the number of working memory errors

relative to ovariectomized control rats (Wide et al. 2004, Daniel and Lee 2004). This finding is consistent with our present finding that a high level of melatonin may decrease estradiol level in females where their learning performance is high. Some studies have, however, provided unequivocal results for the effects of estrogen on learning (Galea et al., 2001; Marriott and Korol, 2003).

5.2. Discussion of Second Study

The results of the second study, which the juvenile hamsters borned to the mothers being exposed to these short and long photoperiods were tested by the same experimental design when they were weaned, can be classified under three main headings: anxiety-like behaviour (in open field apparatus and elevated plus maze), depression (forced swim test) and spatial memory performance (in T-maze).

5.2.1. Anxiety-like behaviours

Both long and short photoperiod groups were more travelled than normal photoperiod groups. This result indicates that day length is affective on the behavioral development of the juveniles. The mothers who gave birth these juveniles received these long, short and normal photoperiod so the juveniles received these applied photoperiods throughout gestational periods. The mothers of these subjects who received three different photoperiods spent more time in the center of the open field in the long and normal photoperiod than in the short photoperiod. This means that less level of anxiety in the long and normal photoperiod than short photoperiod in mothers. These results of the long photoperiod are in good consistent with the results of the juveniles however the short photoperiod decreased anxiety level of juveniles. Some investigations show that dams of some species have the ability to transmit information (maternal transfer) about the day length to their fetuses during the gestational

photoperiod. Maternal transfer of photoperiodic information allows young rodents to make physiological adjustments appropriate for the season of their birth. Maternal transfer of photoperiodic information to the fetus was first reported by Horton in the Montana vole (*Microtus montanus*) (Horton, 1984), then in the Siberian hamster (*Phodopus sungorus*) (Stetson et al., 1986), and in the meadow vole (*Microtus pennsylvanicus*) (Lee and Zucker, 1988). In contrast to these species, gonadal development of prepubertal Syrian hamsters (*Mesocricetus auratus*) is independent of maternal influence (Darrow et al., 1980). In other species, such as the deer mouse (*Peromyscus maniculatus*) and Turkish hamster (*Mesocricetus brandti*), photoperiods during the early postnatal period appear to regulate reproductive development (Gündüz and Stetson, 1998).

Removal of the mother's pineal gland (Elliot and Goldman, 1989) or inhibition of pineal function by constant light in gestation (Horton et al., 1990) prevents this transfer of photoperiodic information. There is further evidence that the rhythm of maternal pineal melatonin secretion is involved in providing the fetus with information about day length (Weaver et al., 1987). Daily injections of melatonin given at selected times of the day to pregnant pineal intact females housed on 16L:8D also yield young with inhibited testicular development when reared in constant light (Horton et al., 1989).

The juveniles born of pinealectomized mothers exhibited less total distance travelled than the juveniles which were born from control mothers in the open field arena. In addition to the total distance travelled information, the juveniles born to pinealectomized mother groups spent less time than the juveniles which were born from control mother groups at the center of open field. Results of the elevated plus maze are supporting the results of the open field data. The juveniles born of

pinealectomized mothers spent less time in open arm of the elevated plus maze than the juveniles which borned from control mothers so pinealectomy increased anxiety level of subjects. This is indicating that in this study, the removal of the pineal gland of the mother is affecting significantly the anxiety level of the juveniles. In the first study, we examined the anxiety level of the mothers which were received three different photoperiods. According to these, in open field and elevated maze tests pinealectomy reduced the anxiety especially in females. The results of the mothers and juveniles are not consistent.

There are to plausible hypothesis explaining transfer of the photoperiodic information from mother to young. According to the first hypothesis, a significant amount of light penetrates the maternal abdomen; thus, the young might receive photoperiodic signals directly by the transmission of light through the maternal abdominal wall (Jacques et al., 1987). In the second hypothesis, it was suggested that the dam might transfer photoperiodic information to the young via hormonal or metabolic pathways. The evidence strongly suggests that the dam provides a signal to the young. Several experiments with pinealectomized dams indicate that the maternal pineal gland is necessary for the transfer of photoperiodic information (Weaver and Reppert, 1986). The successful transmission of photoperiodic information depends on the pineal gland and its hormone melatonin. In the absence of these, no information is transferred to the young, while daily treatment of the pregnant pinealectomized mother with exogenous melatonin led to successful transmission from mother to young of short-day but not long-day information. Our results are consistent with the suggestions of the second hypothesis and support the previous studies that the mother might transfer photoperiodic information to the young via hormonal pathways.

Female juvenile hamsters differed significantly from male juvenile hamsters in the percentage of their total distance travelled on the open field. However the parameters which represent the anxiety level of the subjects such as the time spent at the center of open field and the time spent on the open arms in elevated plus maze do not show significant differences between males and females of juveniles. On the other hand, the mothers of these juveniles were representing a significant sex effect. The anxiety levels of these mothers were lower than the males.

Many of the questions remaining about the mechanism of maternal transfer of photoperiodic information require a fundamental understanding of the mechanism and sites of action of melatonin. It is important to examine the mechanisms by which mammals measure photoperiodic time. To date, only 2 hypotheses have been suggested related to the photoperiodic time measurement of mammals. The duration hypothesis implies that the photoperiod-induced modification in the length of the nocturnal melatonin rise is the message that synchronizes biological and reproductive functions to the different seasons of the year (Reiter, 1987; Bartnes et al., 1993). Evidence in support of this hypothesis has come from melatonin infusions in pinealectomized Siberian and Syrian hamsters (Carter and Goldman, 1983; Maywood et al., 1990). The coincidence hypothesis implies that melatonin exerts an effect only when its circadian secretion is coincident with target tissue sensitivity. This hypothesis supposes that the time of the presence of melatonin is important. Support for this hypothesis has come from experiments in intact adult Syrian hamsters (Stetson and Tay, 1983), Turkish hamsters (Hong and Stetson, 1987), Siberian hamsters (Stetson et al., 1986), pinealectomized adult Syrian hamsters (28), and intact and pinealectomized juvenile Siberian hamsters (Gunduz and Stetson, 2001; Gunduz and Stetson, 2001).

5.2.2. Depression-like Symptoms

In the second study, according to the forced swim test results we could not find statistically significant effects of the photoperiod, sex and pinealectomy in mobility duration of the juveniles. There may be a plausible reason for this result. The mothers (which were coming from first study) of the juveniles were subjected to different photoperiods more than 26 weeks so that we could see the effects of photoperiods on depression on mothers. On the other hand, the time passing for gestation and weaning was very less (only 42 day) and may not be enough for development of the depression-like symptoms in these juveniles. In the first part of the second study, transmission of the anxiety information from mothers to juveniles was very clear in contrast to depression. These may be that the anxiety may become and exit easily but the depression is taking more parameters such as environmental factors and time.

A variety of methods are used to induce models of depression in animals. Some of the common approaches are (1) using stress paradigms, either to native animals or prenatally; (2) breeding for specific phenotypes (3) brain lesions and (4) genetic manipulations (5) monoaminergic mechanism. A discussion of the advantages and disadvantages of these specific methods is beyond the scope of the present review but it is well understood that each of these approaches has its limitations and that all can advance our understanding of the disorder and support the development of novel treatments (Cryan and Mombereau, 2004; Cryan and Slattery, 2007). Interestingly, many of these models, regardless of the way they are induced, demonstrate alterations in behavioral, biochemical and molecular rhythms.

In reproductively photoperiodic rodents, exposure to short days induces changes in affective behaviors that are independent of changes in reproductive hormones. Exposure to short days increases anxiety-like and depressive-like responses in collared

lemming (Weil et al., 2007) and Siberian hamsters (Predergast and Nelson, 2005; Pyter and Nelson, 2006). These photoperiodic behavioral changes develop early during short-day exposure (Predergast and Nelson, 2005) and can persist after maximal gonadal regression (Pyter and Nelson, 2006; Weil et al., 2007) supporting the idea that the influence of photoperiod on affect can be independent of circulating gonadal steroids. Further support of this idea comes from a growing body of evidence showing that animals that do not respond reproductively to photoperiod also display photoperiodic response (Nelson, 1990; Sumova et al., 2004). Short-day exacerbation of depressive-like and anxiety-like behaviors have been reported in both nocturnal rodents (rats (Benabid, 2008; Molina-Hernandez et al., 2000)), and diurnal rodents (e.g., Nile grass rats (Ashkenazy-Frolinger et al., 2010)) and sand rats (Ashkenazy-Frolinger et al., 2009; Ashkenazy-Frolinger et al., 2009). These affective responses to short days are unambiguously linked directly to pineal melatonin secretion duration (Ashkenazy-Frolinger et al., 2009), which may model the extended duration of melatonin secretion observed in humans with seasonal affective disorder (Wehr et al., 2001).

Photoperiod affected the frequency of mobility and velocity. Juveniles born from mothers were subjected to long photoperiod were more depressive than the juveniles born from mothers who were subject to short and normal photoperiods. It has been shown previously that short-day housed male Siberian hamsters exhibit elevated anxiety-like and depressive-like behaviors (Prendergast and Nelson, 2005). These behaviors are influenced not only by acute short-day photoperiod exposure but also by prenatal melatonin exposure in utero, suggesting that photoperiodic exposure of the mother during gestation may organize the developing brain via exposure to the

mother's melatonin rhythms, influencing subsequent adult affective responses (Workman et al., 2008).

We found an interaction effect of photoperiod and pinealectomy in mobility duration in this study. The juveniles born of pinealectomized mothers showed high mobility than the juveniles which born of control mothers in short and normal photoperiod. However, this trend was the opposite in long photoperiod. When we examined the depression in mothers we see that they were more mobile in short photoperiod than in long and normal photoperiod. Pinealectomized subjects were more mobile than controls. Pinealectomy decreased depression. This means that pinealectomy decreased depression in males but did not affect it in females.

There was another interaction effect between treatment and sex. Pinealectomy decreased mobility duration in males. Male juveniles born to controls mothers spent more time in mobile female juveniles born from controls mothers in control groups.

5.2.3. Spatial Memory Performance

In the second study, we found an interaction effect between the photoperiod and sex. Female juveniles spent more time than male juveniles for finding award in normal photoperiod. On the other hand, male juveniles spent more time than female in short photoperiod. There was no differences between the males and females in long photoperiod. Pyteret et al (Pyteret et al., 2008) have shown that, when the rodents were subjected to a short-day photoperiod, spatial learning performance is impaired and hippocampal plasticity altered. Furthermore, the neurogenesis of the hippocampus is effected by short-day photoperiod exposure and water maze experience together. As well as altering cognition and its neural substrates, short-day photoperiod exposure influences affective state. Changes in brain morphology in *P. leucopus* following

exposure to short day lengths are accompanied by impaired spatial learning and memory in the Morris water maze (Pyter et al., 2005a, 2006; Workman et al., 2009). Spatial learning and memory is correlated with hippocampal long-term potentiation (LTP; Shapiro and Eichenbaum, 1999; Lynch, 2004), such that LTP is induced in the hippocampus during learning (Whitlock et al., 2006), inhibition of LTP impairs performance in spatial learning tasks (Morris et al., 1986), and LTP maintenance in the hippocampus is required for retention of spatial memory (Pastalkova et al., 2006). LTP, a measure of increased efficiency of synaptic transmission following high-frequency stimulation (Bliss and Gardner-Medwin, 1973), is the strongest candidate for a synaptic mechanism by which new memories are formed and stored in the brain (Bliss et al., 1993; Malenka, 2003). Short days decrease the amplitude of LTP in the CA1 region of the hippocampus *in vitro* and impair spatial learning and memory in the Barnes maze.

In consistent with our results, Bucci et al (1995) found no sex difference in latency to find the platform for male and female rats aged approximately 26 weeks, and suggested that the age of the animal contributes to sex differences. Harris et al. (Harris et al., 2009) has found also that there is no sex difference between younger as 14–15 weeks old rats. The authors suggest that the younger rats of each sex were equally affected by the stress of the test as they displayed equivalent thigmotactic behaviour; whilst the older rats were differentially affected by the acute stress of the test itself.

When we examined the spatial memory performance of the mothers, we see that the sex was significant on the total time spent for finding award and also photoperiod was significant. The mothers were not affected from pinealectomy. It is well recognized that the removal of the pineal gland abolishes the rhythmic endogenous

melatonin release and decreases the plasma levels of melatonin significantly (Hoffman and Reiter, 1965). Parallel to studies on the effects of regulatory function of melatonin on the learning performance, pinealectomy has been received a research attention in the literature. For instance, one research has shown that pinealectomy itself did not have a detrimental effect on cognitive performance in rats, whereas the interaction of it with the other lesion (i.e, lesion on habenula) did impair cognitive performance (Lecourtier et al., 2005). A great number of studies have consistently demonstrated that pinealectomy did not have a significant role on the acquisition and extinction of the active avoidance behavior (Appenrodt and Schwarzberg, 2003), anxiety behavior (Appenrodt and Schwarzberg, 2000), passive avoidance learning (Appenrodt and Schwarzberg, 1999), open field exploratory activity (Kovács et al., 1974), and social recognition (Appenrodt et al., 2002).

There may be some hormonal effects between the adults and the juveniles. Prepubertal males clearly preferred a stimulus–response strategy over a place strategy, indicating that the choice of learning strategy in males is affected by the age of the learner. The lower levels of testosterone characteristic of pre pubertal males (Little et al., 1992) may have exacerbated the stress response to the mildly aversive water environment used to assess learning strategy (Seale et al., 2004a; Seale et al., 2004b; Viau and Meaney, 1996). Consequently, an increased stress response may have heightened anxiety, biasing pre pubertal male rats toward a stimulus–response learning strategy.

5.3. Discussion of Third Study

The results of the third study, which rats were SCN-lesioned and sham-SCN-lesioned and intact were tested by the same experimental design, can be classified under three main headings: anxiety-like behaviour (in open field apparatus and elevated plus maze), depression (forced swim test) and spatial memory performance (in Morris water maze).

5.3.1. Anxiety-like behaviours

Groups were more travelled at 12:00 than groups at 24:00 in the open field. There were significant differences between time 12:00 hr between the time 18:00 hr. Group of time 12:00 hr spent the highest time in the center of the the open field. There were significant differences between control and SCNx. SCNx were less anxious because SCNx groups spent more time at the center than Sham-SCNx and control. The results of the elevated plus maze has shown that subjects spent more time than the others in open arms at 18:00 hr. In this group had low anxiety level. SCNx groups which were less anxious spent more time than control and Sham-SCNx. These results were parallel results of open field.

In a previous study, (Kaya et al.,2011) examined the effects of the time of the day and the pinealectomy on anxiety-like behaviour in male Wistar rats by using elevated plus maze open field. Experiments were performed with control and pinealectomy groups at the four different time points (06:00, 12:00, 18:00 and 24:00 hours; LD 12:12, lights on at 06:00 and off at 18:00). In open field, the main effect of the measurement time was significant on the total distance travelled, the mobility and the velocity. In elevated plus maze, the main effect of the measurement time was

significant on the total distance travelled, the total entry to closed arms, and mobility. The main effect of the pinealectomy was insignificant on all of the measured parameters in both open field and elevated plus maze except for the total entry to closed arms in elevated plus maze. The results of the present study showed for the first time that the time of the day when the measurements are performed is important on the anxiety like behavior of the Wistar albino rats. The results of the present study are consistent with the results of this previous study.

Pineal melatonin is important in the mammalian circadian organization. It has also been shown that pineal gland plays important roles in the regulation of the seasonal variation of the anxiety like behaviour (Naranjo-Rodriguez et al., 2000; Papp et al., 2006). Although, pinealectomy did not change the circadian rhythms such as locomotor activity rhythm in both free-running and light-dark cycle conditions in rats (Quay, 1970), several studies have shown the influence of melatonin on the regulation of the circadian rhythms in mammals (Laakso et al., 1992; Marumoto et al., 1996a; Marumoto et al., 1996b; Sharma, 2003). The finding that pinealectomy alone did not have a significant effect on anxiety behavior is consistent with other research findings (Kovács et al., 1974; Juszczak et al., 1996), suggesting that the pineal gland is not basically involved in the behavioral performance.

There is evidence in the literature that suggesting the interaction of melatonin with central gammaaminobutyric acid (GABA) neurotransmission. Melatonin has been shown to enhance the GABA in rat brain tissue in vitro (Niles et al., 1987; Coloma and Niles, 1988). When melatonin was applied in vivo, it increased the GABA levels in several brain regions in rats (Rosenstein and Cardinali, 1986; Xu et al., 1995). The release of the melatonin hormone in rats shows a diurnal pattern which is high throughout the darkness (Illnerova et al., 1983). However, in pinealectomy the rhythm

of melatonin is abolished (Hoffman and Reiter, 1965). There is a reciprocal relationship between SCN and melatonin. SCN is generating and controlling the circadian rhythm of melatonin while melatonin is acting on SCN as a negative feedback agent in order to control the activity of SCN. Thus the future research should examine the effects of exogenous melatonin administration to rats after pinealectomy.

The effect of disturbances of circadian rhythmicity on emotional behaviour is less clear (Jones and King, 2001). In rodents, alterations in the phase period or amplitude of hypothalamic–pituitary–adrenal axis hormones, melatonin, body temperature, locomotor activity and drinking rhythms have been observed in several models of depression (Solberg et al., 2001). Very few studies, which for the most part have been performed on rats, have attempted to determine the effect of a dysfunctional circadian pacemaker on emotional behavior or stress responsiveness. SCN lesions (Arushanian and Beier, 1999) or a mutation of the cAMP-responsive element modulator (Maldonado, 1999) were shown to alter levels of anxiety and locomotor activity. A mutation of the circadian gene–Clock–leads to increased exploratory behaviour and activity-based arousal in the open field test and in the elevated plus maze (EPM), but is not limited to the emotional component of arousal that is elicited by novel and stressful environments produced in the EPM. Conversely, dysfunction of the Clock gene does not lead to depressive-like behaviour in the forced swimming test. Easton et al. (Easton et al., 2003) suggest in their study that clock function may influence anxious behaviour in some situations but does not have a pervasive nor consistent effect on anxiety. Easton et al. (Easton et al., 2002) have also reported that the clock mutation increases wakefulness even in the absence of the SCN indicating that the role of clock in the regulation of arousal is independent from its role in circadian pacemaker function.

It is suggested that individual members of the central circadian clock may have separate functions in regulating a range of mood-anxiety-and-reward-related behaviors, perhaps through expression outside of the central circadian pacemaker of the SCN (McClung, 2011).

5.3.2. Depression-like Symptoms

Two separate studies found that bilateral SCN lesions in rats lead to a reduction in depression-related behavior in the forced swim test (Arushanian and Popov, 1994). However, a study by Tuma et al. (Tuma et al., 2005) found that lesions of the SCN had no effect on depression and anxiety-related behavior following social defeat stress, but SCN integrity was necessary for the effective antidepressant actions of agomelatine (Tuma et al. 2005). Thus, in certain paradigms, destruction of the SCN might lead to an antidepressant phenotype, and in others it is necessary for an antidepressant response. These results may not be at odds with each other since agomelatine is known to inhibit SCN neuronal firing, thus a reduction in SCN activity could be antidepressant (Ying et al. 1996). However, as mentioned previously, other regions outside of the SCN are obviously involved in the baseline response to social defeat.

5.3.3. Spatial Memory Performance

It has been shown that the activation in the left parahippocampus at 22:00 h was greater in subjects who had passed the melatonin onset phase. Parahippocampal activation correlated with individual endogenous melatonin levels and was not further affected by exogenous melatonin. These results demonstrate that memory related activation in the hippocampus and parahippocampus are affected by time of day and melatonin in a differential manner and may implicate the circadian clock and melatonin in human memory processing during the night (Gorfine and Zisapel, 2007).

Furthermore, melatonin appears to be involved in certain aspects of memory processing. In related brain imaging studies, Gorfine et al. (Gorfine et al., 2007) found that the exogenous administration of melatonin was as effective as a 2 h mid-day nap for enhancing performance in a verbal association task, thus demonstrating that melatonin has an important role in memory consolidation.

The neural substrate that has been related to performance in aversive conditioning tasks is the amygdaloid complex (Vazdarjanova and McGaugh, 1999; Nader et al., 2000; Barros et al., 2005; Herdade et al., 2006; Canal 2007). It is interesting to mention that there is an indirect anatomic pathway between the SCN and the amygdala. The central and basolateral nucleus of the amygdala exhibit opposite diurnal rhythms of clock *Period2* protein expression, with such expressions becoming arrhythmic when the SCN is lesioned (Lamont et al 2005). We should also keep in mind that emotionality has been shown before to be affected by circadian rhythm disruption; for example, negative effects on mood are common in humans (Parkes, 2002).

6. CONCLUSION

In the literature, there was no comprehensive study which examines the reciprocal relationship among SCN, pineal gland, melatonin and mood state and it was not known yet the practical and theoretical results of this relationship. Our results indicate that long photoperiod and pinealectomy reduced the anxiety, depression, and improved spatial learning in the first study. These results of the first study may shed lights on some inconsistencies of the findings of the previous studies with regard to the effects of relationship between photoperiod and mood state. In the second study, whether there was an effect of the maternal transfer on behaviors or not were tested. The results of the second study suggest that behavior of the anxiety was transferred to the juveniles but not the depression, and spatial memory. Our last study was planned to investigate whether or not behaviors have a circadian rhythm and this rhythm is controlled by the SCN or not. The results of the third study indicated that SCN lesions changed the circadian rhythms of the anxiety, depression, and spatial memory. Lesion groups had low anxiety level but this situation was not the same with result of spatial memory test. Taken together, these results are unique contribution to the fields of behaviors and photoperiod.

7. REFERENCES

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